NITROGEN AND SULPHUR ANALOGUES OF EPOXY AND HYDROXY ACIDS

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A. INTRODUCTION

This chapter is concerned with a discussion of the chemistry of nitrogen and sulphur substituted fatty acids in which the substituents are located at internal positions of the fatty acid chain. This rather sharp focus eliminates from our field of view a major portion of the known nitrogen and sulphur derivatives of fats, particularly such familiar materials as long-chain amides, amines, nitriles and thioacids obtainable by the derivatisation of the carboxyl function. We shall further ignore fatty acid derivatives in which the sulphur or nitrogen

substituent is located in the *alpha* or *omega* position, and thus our concern will centre on that portion of the fatty acid chain which is most characteristic of the aliphatic hydrocarbon structure. In a sense, then, this discussion deals with the formation and reactions of long-chain aliphatic nitrogen and sulphur compounds in which the substituent can be found at secondary carbon atoms.

Until recently, oxygen played a fairly unique role as a substituent on fatty acid chains. Epoxides, hydroxides, hydroperoxides, and ketones, to name just a few, were well known and thoroughly characterised derivatives which had been synthesised, and many of which had been found in naturally occurring lipid materials, mostly in plant oils. On the other hand, fatty acid derivatives chain substituted by nitrogen or sulphur were, with few exceptions, rather obscure laboratory curiosities, and none had apparently been found in natural sources. Lipid materials such as sphingolipids do, of course, contain sulphur and nitrogen, but not at mid-chain locations.

During the past few years considerable interest has developed in the synthesis and reactions of alkyl-substituted heterocyclic small-ring compounds, including those derived from unsaturated fatty acids. New methods of synthesis, including photochemical procedures, are now beginning to make fatty aziridines, and, to a lesser extent, fatty episulphides, readily available. The formation and reactions of these heterocyclic compounds, and of other nitrogen- and sulphur-bearing fatty materials actually or theoretically derivable from these small ring species are the subjects to be discussed.
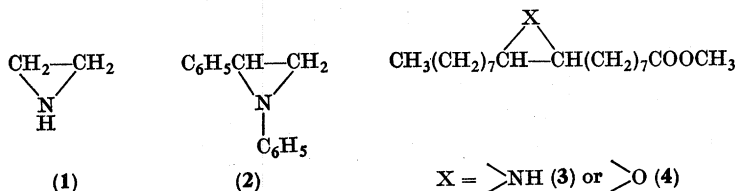
B. NITROGEN COMPOUNDS

1. Introduction

Classical methods of substituting nitrogen in the fatty acid chain have entailed the addition of nitrogen oxides, amines, nitriles and other nitrogenous species to the double bonds of unsaturated fatty acids. These methods, some of which are outlined in Section B3, were, for various reasons, not entirely satisfactory for the synthesis of, for example, amino fatty acids. On the other hand, it has long been apparent that 2,3-dialkylaziridines are potentially useful intermediates leading to amines or substituted amines in which nitrogen is bonded to secondary carbon atoms, but the necessary epimino-substituted fatty acids were not readily obtainable and in fact had not yet been synthesised.

In recent years new synthetic methods, especially those involving pseudohalogen additions to olefins, have been perfected and have led to practical procedures by which epimino-substituted fatty acid derivatives can be prepared. These nitrogen analogues of the familiar epoxidised fatty acids constitute a new class of chemically modified fatty acids. The importance of these compounds is expected to increase as preparatory methods improve and as the reactions of these compounds are elucidated. Because of the importance and the recency of the information, a significant portion of this chapter is devoted to a discussion of the synthesis and reactions of aliphatic aziridines in general and to fatty epimino derivatives in particular.

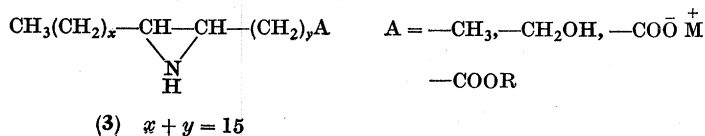## 2. Aziridines

(a) Nomenclature

The name *aziridine* is generally applied to compounds containing the three-membered, saturated ring present in the parent compound, ethylenimine (1). Simple derivatives of (1) are named as aziridines, e.g. 1,2-diphenylaziridine (2), but for more complex compounds it is more convenient to consider the nitrogen bridge as a substituent. For

$$CH_2\text{---}CH_2 \qquad C_6H_5CH\text{---}CH_2 \qquad CH_3(CH_2)_7\overset{X}{CH}\text{---}CH(CH_2)_7COOCH_3$$
$$\underset{H}{\underset{N}{\diagdown\diagup}} \qquad \underset{\underset{C_6H_5}{N}}{\diagdown\diagup}$$

$$\text{(1)} \qquad\qquad \text{(2)} \qquad\qquad X = \text{>NH (3) or >O (4)}$$

instance, (3) is named methyl *cis*-9,10-epiminooctadecanoate, rather than 2-octyl-3(7-carbomethoxyheptyl)aziridine. This nomenclature, which will be followed in the present chapter, is entirely analogous to that used in naming methyl *cis*-9,10-epoxystearate (4).

(b) Properties

The properties and reactions of ethylenimine and its lower alkyl and aryl derivatives have been discussed in two excellent reviews (Fanta, 1964; Gembitskii, Loim, and Zhuk, 1966). The higher aliphatic, internal aziridines (3) are colourless, crystalline solids (Table 1), and

$$CH_3(CH_2)_x\text{---}CH\text{---}CH\text{---}(CH_2)_yA \qquad A = \text{---}CH_3, \text{---}CH_2OH, \text{---}CO\overset{-}{O}\,\overset{+}{M}$$
$$\underset{H}{\underset{N}{\diagdown\diagup}}$$
$$\text{---COOR}$$

$$\text{(3)} \quad x + y = 15$$

the *trans* isomers generally melt lower than the *cis*. The epimino derivatives are readily purified by thin-layer, adsorption, or vapour-phase chromatography or by crystallisation from polar solvents. The solids can be stored at room temperature without special precautions

TABLE 1

Long-chain aliphatic aziridines

$$\underset{\displaystyle R-CH-CH-R'}{\overset{\displaystyle \overset{H}{N}}{\bigwedge}}$$

R	R'	Isomer	mp, °C	Reference[1]
$CH_3(CH_2)_7$	$(CH_2)_7CH_3$	*cis*	65·0–66·0	a
			63·5–64·0	b
			63·0–64·0	d
$CH_3(CH_2)_7$	$(CH_2)_7CH_3$	*trans*	48·0–50·0	a
			48·0–49·0	b
			47·0–48·0	d
$CH_3(CH_2)_{10}$	$(CH_2)_4CH_3$	*cis*	60·0–62·0	d
$CH_3(CH_2)_{10}$	$(CH_2)_4CH_3$	*trans*	43·0–44·0	d
$CH_3(CH_2)_{11}$	$(CH_2)_7CH_3$	*cis*	61·0–63·0	d
$CH_3(CH_2)_{11}$	$(CH_2)_7CH_3$	*trans*	45·0–47·0	d
$CH_3(CH_2)_7$	$(CH_2)_7CH_2OH$	*cis*	71·5–72·5	a
			70·0–71·0	d
$CH_3(CH_2)_7$	$(CH_2)_7CH_2OH$	*trans*	61·0–62·0	a
			62·0–63·0	d
$CH_3(CH_2)_{10}$	$(CH_2)_4CH_2OH$	*cis*	78·0–79·0	d
$CH_3(CH_2)_{10}$	$(CH_2)_4CH_2OH$	*trans*	64·0–66·0	d
$CH_3(CH_2)_{11}$	$(CH_2)_7CH_2OH$	*cis*	84·0–85.0	d
$CH_3(CH_2)_{11}$	$(CH_2)_7CH_2OH$	*trans*	76·0–77·0	d
$CH_3(CH_2)_7$	$(CH_2)_7COOCH_3$	*cis*	50·0–51·0	b
$CH_3(CH_2)_7$	$(CH_2)_7COOCH_3$	*trans*	40·0–41·0	b
$CH_3(CH_2)_7$	H	—	bp 52·0–52·5/0·05	c
$CH_3(CH_2)_9$	H	—	bp 70·0—71·0/0·1	c
$CH_3(CH_2)_{15}$	H	—	51·5–52·5	c
$CH_3(CH_2)_7$	$(CH_2)_7COOK$	*cis*	242–245	a

[1] *Key to references.* (a) Gebelein, Swift, and Swern (1967). (b) Foglia, Smith, and Maerker (1970). (c) Foglia and Swern (1967). (d) McGhie and Warren (1968).

and do not appear to absorb carbon dioxide or moisture from the atmosphere. The i.r. spectra of crystalline (3) show strong adsorption bands at 3100–3200 cm^{-1} (N—H) and at 800–900 cm^{-1} (ring C—H) which are absent in the melted sample or in its solutions (Foglia, Smith, and Maerker, 1970).

Because of the steric constraints on the substituted three-membered ring, the nitrogen atom inversion may be slowed or even prevented in some compounds. Thus the possibility of the existence of optical isomers of N-alkylaziridines must be considered. It has been shown by NMR techniques (Bottini and Roberts, 1956) that the normal inversion rate of trialkylamines is indeed decreased in N-alkyl-aziridines, and that N-halo- as well as N-aminoaziridines do exist as stable and distinguishable pyramidal structures at room temperature (Brois, 1968).

Ethylenimine is known to be a highly toxic material which is corrosive to the skin and readily absorbed in toxic amounts. Serious illness may result from ingestion of relatively small amounts. In the absence of published data regarding the physiological activity of the higher aziridines, they must be considered toxic and should be treated with care. In view of the bacteriostatic and fungistatic activity of numerous fatty amines (Hueck, Adema, and Wiegmann, 1966) and because of the presence of some epimino functions in some antibiotics (Patrick, Williams, Meyer, Fulmor, Cosulich, Broschard, and Webb, 1964), the discovery of some beneficial physiological properties of fatty aziridines would not be too unexpected. However, the reputation of the lower aziridines as carcinogenic alkylating agents (Walpole, 1958) cannot be ignored.

(c) Synthesis

(*i*) *From olefins via pseudohalogen adducts.* A resurgence of interest in the chemistry of aliphatic compounds bearing nitrogen on secondary carbon atoms has been evident in the 1960's. Much of the research activity has centred on the addition of a group of reagents loosely classified as 'pseudohalogens' to the double bonds of aliphatic and alicylic compounds. The term 'pseudohalogen' is generally applied to some reagents which add to olefinic double bonds in a manner similar to that of halogen molecules and which often contain halogen in one of its lower oxidation states. The reaction is generalised in

$$\text{XN} + \left[\quad \longrightarrow \quad \overset{\text{X}}{\underset{\text{N}}{\bigg]} \right. \tag{1}$$
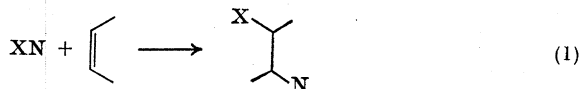
equation (1). X is often iodine and less commonly bromine or chlorine, while N is sometimes a nucleophilic group containing nitrogen, such as isocyanate or azide.

Iodine isocyanate (INCO) is a pseudohalogen which has recently come into prominence. It was first prepared in 1930 (Birckenbach and Linhard, 1930) and its reactions with some olefins were studied (Birckenbach and Linhard, 1931), but subsequently the compound and its reactions were apparently forgotten until revived by Drefahl and Ponsold (1960) almost 30 years later. In its normal use, INCO is prepared *in situ* from iodine and excess silver cyanate (equation (2)):

$$AgCNO + I_2 \rightleftharpoons INCO + AgI \qquad (2)$$
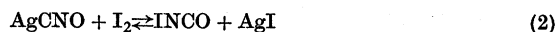
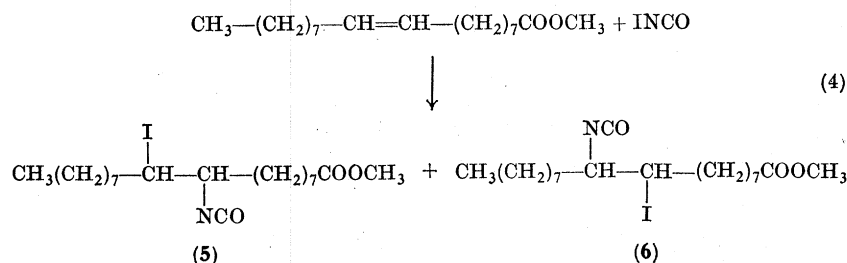The preparation is carried out in ether, tetrahydrofuran or other, similar solvents and in the presence of the olefin. An excess of silver cyanate is utilised to drive the INCO generation to completion. An alternative to this is the preparation of INCO in the absence of olefin in cold solvents (0° to −60°) and addition of the olefin to the preformed INCO solution. An increase in reactivity toward certain types of olefins is achieved in this manner, but even cold solutions of the reagent are fairly unstable and cannot be preserved for long periods without loss in activity. Rosen and Swern (1966) have studied the analysis, stability and reactivity of dilute solutions of iodine isocyanate in various solvents.

The addition of INCO to isolated double bonds proceeds rapidly, is stereospecific, and occurs in a *trans* manner (Hassner and Heath-cock, 1964, 1965) (equation (3)). The reaction is assumed to proceed

$$\mathrm{>C{=}C<} + INCO \longrightarrow \mathrm{>C{-}C<} \longrightarrow \mathrm{>C{-}C<} \qquad (3)$$
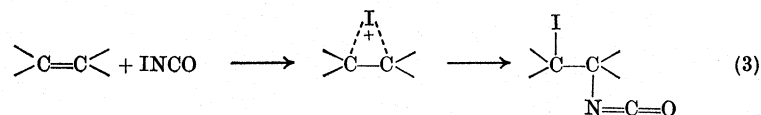
by way of a cyclic iodonium ion (Gebelein, Rosen, and Swern, 1969) which is attacked by the isocyanate anion at the most highly substituted carbon. This regiospecificity (Hassner, 1968) is reminiscent of the Markownikoff addition of hydrogen halides to unsymmetrical olefins and obeys the same principles. The immediate surrounding of the double bond of monounsaturated fatty acids is, of course, essentially symmetrical, and the addition of iodine isocyanate to oleic acid or its derivatives is expected to produce two positional isomers (5) and (6) as indicated in equation (4) for methyl oleate.

It has been tacitly assumed, but never established, that products such as (5) and (6) are found in equal amounts, but there is little reason to doubt this assumed isomer distribution.

$$CH_3\text{---}(CH_2)_7\text{---}CH\!=\!CH\text{---}(CH_2)_7COOCH_3 + INCO$$

$$\downarrow \tag{4}$$

$$\underset{\underset{NCO}{|}}{CH_3(CH_2)_7\text{---}\overset{\overset{I}{|}}{CH}\text{---}CH\text{---}(CH_2)_7COOCH_3} \quad + \quad \underset{\underset{I}{|}}{CH_3(CH_2)_7\text{---}\overset{\overset{NCO}{|}}{CH}\text{---}CH\text{---}(CH_2)_7COOCH_3}$$

$$(5) \hspace{5cm} (6)$$

The analogy between the reactions of olefins with INCO and with hydrogen halides is, however, not unfailing and must be applied with caution. It has been observed (Hassner, Lorber, and Heathcock, 1967), for instance, that in the addition to hex-1-ene INCO gives a mixture of the two positionally isomeric products, while, of course, hydrogen halides give the secondary halide almost exclusively.

The β-iodoisocyanates are a rather reactive species which, in the normal course of aziridine synthesis, are not isolated, but are converted to β-iodocarbamates by treatment with an alcohol, usually methanol (equation (5)).

$$\underset{\underset{NCO}{|}}{\overset{\overset{I}{|}}{>\!C}\text{---}C\!<} \quad + \quad CH_3OH \quad \longrightarrow \quad \underset{\underset{NHCOOCH_3}{|}}{\overset{\overset{I}{|}}{>\!C}\text{---}C\!<} \tag{5}$$
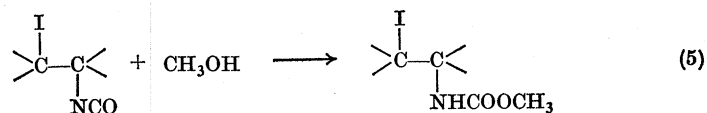
The β-iodocarbamates are fairly stable, and the lower molecular weight homologues can be purified by distillation; however on prolonged storage these compounds slowly convert to 2-oxazolidones. The cyclisation can be accelerated by heating at 150–180° and is assumed to proceed by the mechanism shown in equation (6). Oxazolidone formation is discussed further on pages 168–170.

$$(6)$$
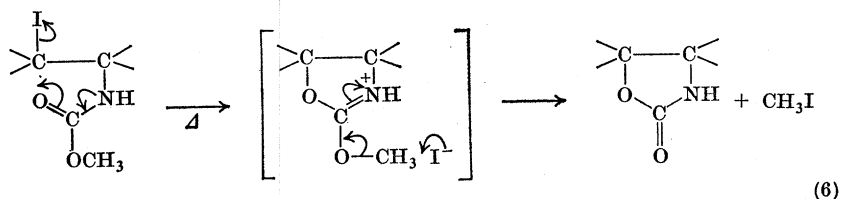
Treatment of β-iodocarbamates with strong base results in ring closure and formation of aziridines. Cyclisation is normally carried out in methanolic potassium hydroxide and requires three equivalents of base (equation (7)).

$$\overset{+}{\underset{\substack{\text{N}-\text{H} \\ | \\ \text{COOR}}}{\overset{\text{I}}{\underset{\;}{\text{C}-\text{C}}}} \quad \xrightarrow{} \quad \overset{\text{C}-\text{C}}{\underset{\substack{\text{N} \\ | \\ \text{COOR}}}{}} \quad \xrightarrow{\;2\,\text{OH}^-\;} \quad \overset{\text{C}-\text{C}}{\underset{\substack{\text{N} \\ | \\ \text{H}}}{}}$$

$$+\,\text{ROH} + \text{CO}_3^= \qquad (7)$$
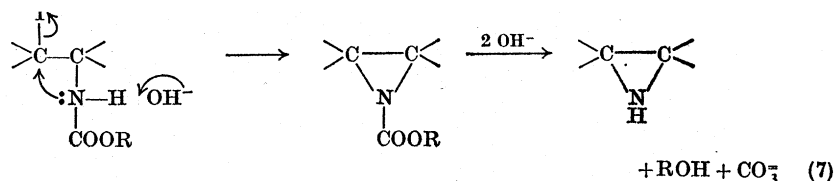
A detailed study of the cyclisation reaction (Hassner and Heathcock, 1964) has demonstrated that ring closure to the aziridine precedes hydrolysis to the carbamic acid. It is notable that primary or secondary carbamates which have no halogen on the β-carbon are difficult to hydrolyse under similar conditions.

The ring closure step apparently is a concerted reaction and occurs with inversion at the carbon atom bearing halogen (equation (7)). Thus, elimination of the elements of hydrogen iodide from the *threo*-β-iodocarbamate causes formation of the *cis*-aziridine. The overall synthesis starting with olefin and ending with aziridine contains two inversion steps, so that a *cis*-aziridine is obtained from a *cis*-olefin and a *trans*-aziridine from a *trans*-olefin.

A series of fatty acid derivatives containing an internal aziridine group has been synthesised by the INCO procedure (Gebelein, Swift, and Swern, 1968). The compounds prepared were potassium *cis*-9,10-epiminooctadecanoate, *cis*- and *trans*-9,10-epiminooctadecan-1-ol and *cis*- and *trans*-9,10-epiminooctadecane. The pure aziridines were shown to have characteristic infrared absorption bands. The *cis*-aziridines have strong bands at 3200 cm^{-1} and at 855 cm^{-1} while *trans*-aziridines absorb at 3150 cm^{-1} and at 885 cm^{-1} (Foglia *et al.*, 1970b). These bands appear only in the crystalline state and vanish when the sample melts or is dissolved. More recent work indicates that some of these characteristic bands may not be linear with concentration.

An interesting development which emerged from the work of Gebelein is that *trans*-olefins give relatively poor yields of *trans*-aziridines by the iodine isocyanate method. For instance, *cis*-9,10-epiminooctadecane was obtained in 47 per cent yield from *cis*-9-octadecene, while the yield of the corresponding *trans* isomer was only 18 per cent. This gross difference in yields has also been observed in other laboratories, but the reason for it is not clear. Some experimental evidence indicates that iodine isocyanate adds more reluctantly to long-chain internal *trans* olefins than to the corresponding *cis* isomers. Evidence to the contrary, however, can be found in the rate studies of Gebelein and Swern (1968) which indicate (by olefin

disappearance) that methyl oleate adds INCO only about 14 per cent faster than methyl elaidate. Steric inhibition during the ring closure step or difficulties with hydrolysis of the β-iodocarbamate have both been cited as possible causes of the low yields of *trans*-aziridines. However, the arguments in support of these views are not very strong and suffer further when one compares the ring closure reactions of the *erythro*-β-iodocarbamates with those of the corresponding *erythro*-β-chlorocarbamates (see below).

The reactivity of a wide variety of olefins toward INCO addition has been examined (Rosen and Swern, 1966; Hassner *et al.*, 1967; Gebelein and Swern, 1968; Gebelein *et al.*, 1969; Grimwood and Swern, 1967). Among these have been some dienes, acetylenes and allenes, but the reaction of INCO with skipped double bond systems such as are found in polyunsaturated fatty acids has not been studied.

Another pseudohalogen which may become important in the synthesis of fat-derived aziridines is N,N-dichlorourethane (DCU). This reagent has been known even longer than INCO (Datta and Gupta, 1915; Houben, 1922), but its synthesis was placed on a practical basis only when its reactions were studied in some detail (Foglia and Swern, 1966). The reagent is prepared in analytical purity in 80 per cent yield by reaction of the calculated quantity of chlorine with urethane in buffered aqueous solution (equation (8)). The product

$$\underset{\text{C}_2\text{H}_5\text{O}\overset{\text{O}}{\overset{\|}{\text{C}}}-\text{NH}_2 + 2\text{Cl}_2}{} \xrightleftharpoons[]{\text{NaOAc—HOAc}} \underset{\text{C}_2\text{H}_5\text{O}-\overset{\text{O}}{\overset{\|}{\text{C}}}-\text{N}\overset{\diagup\text{Cl}}{\underset{\diagdown\text{Cl}}{}} + 2\text{HCl}}{} \qquad (8)$$
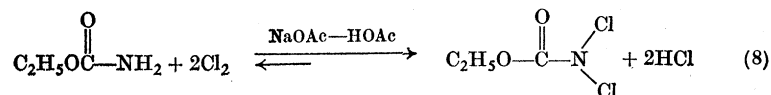
separates from the aqueous system as a yellow oil and is distilled to provide an analytically pure sample. DCU is fairly stable when protected from light, and although it is normally stored in the refrigerator it loses positive chlorine only slowly at room temperature.

The addition of DCU to olefins has been investigated in a series of studies (Foglia and Swern, 1966, 1967, 1968) which have established that the reaction has many of the characteristics of a free radical addition reaction but is strongly influenced by electronic and steric effects. The formation of the β-chloro-N-chlorocarbamate from DCU and a typical olefin is envisioned to occur by the sequence of events shown in Scheme I. The N-chloro-β-chloroalkylcarbamates are not isolated but are reduced to the β-chloroalkylcarbamates with aqueous bisulphite.

Addition of DCU to terminal aliphatic olefins proceeds in an anti-Markovnikoff manner and is subject to steric retardation by alkyl

groups attached to the carbons forming the double bond. Addition to cyclohexene gives the expected 2-chlorocarbamates (both *cis* and *trans*) and considerable quantities of the three positionally isomeric chlorocyclohexenes. Yields of DCU adducts of terminal and internal olefins are in the 50–65 per cent range and are probably capable of improvement. The results obtained with cyclohexene lead to the expectation that yields of addition products should decrease, and allylic products increase, as the number of allylic hydrogens increase.

Addition of DCU to *trans*-hex-3-ene gives a mixture of about equal amounts of *erythro* and *threo* isomers, in accordance with the free-radical character of this reaction. More recent studies of DCU addition to *cis*- and *trans*-octadec-9-ene and methyl *cis*- and *trans*-octadec-9-enoate indicate (Foglia *et al.*, 1970b) that mixtures of *erythro* and

SCHEME I

$$C_2H_5OCONCl_2 \rightarrow C_2H_5OCO\overset{\cdot}{N}Cl + Cl\cdot$$
$$\text{DCU} \qquad\qquad\qquad (7)$$

$$(7) + R\text{---}CH\text{=}CH_2 \rightarrow R\text{---}\overset{\cdot}{C}H\text{---}CH_2\text{---}NClCOOC_2H_5$$
$$(8)$$

$$(8) + \text{DCU} \rightarrow R\text{---}CH(Cl)\text{---}CH_2\text{---}NClCOOC_2H_5 + (7)$$
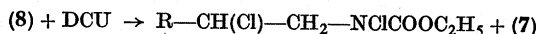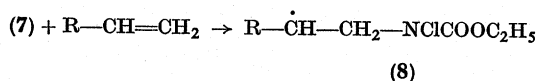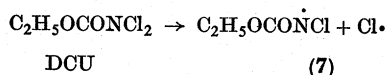
threo isomers are also obtained from these olefins. Cyclisation of the adduct mixture with base gives a product containing more *trans* than *cis* aziridine, regardless of the geometry of the starting olefin. This leads to the conclusion that in the cyclisation of the β-chlorocarbamate the *erythro* form does not experience materially more difficulty than the *threo* isomer.

At the present state of technology, aziridines are prepared from *cis*-olefins in slightly lower yields (10–15 per cent lower) by the DCU route than by the INCO method. For *trans* olefins this relationship is reversed. At this time there is no satisfactory explanation for the low yields of *trans* aziridines from *trans* olefins by the INCO procedure.

Pyrolysis of β-halocarbamates, chloro or iodo, leads to the formation of substituted 2-oxazolidones. When the carbamate is formed from an aliphatic, terminal olefin the substituent is an alkyl group which may be located either in the 4- or the 5-position of the oxazolidone, i.e. the products are either (9) or (10), depending on the relative position of the halogen and nitrogen substituents in the carbamate.

$$
\begin{array}{cc}
\overset{(4)\quad(5)}{\underset{\displaystyle \underset{\text{O}}{\parallel}}{\underset{\text{HN}\diagdown\underset{\text{C}}{}\diagup\text{O}}{\text{R—CH—CH}_2}}} & \overset{(4)\quad(5)}{\underset{\displaystyle \underset{\text{O}}{\parallel}}{\underset{\text{HN}\diagdown\underset{\text{C}}{}\diagup\text{O}}{\text{CH}_2\text{—CH—R}}}} \\
(9) & (10)
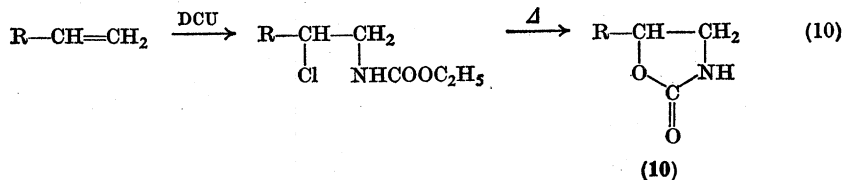\end{array}
$$
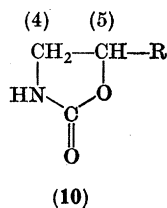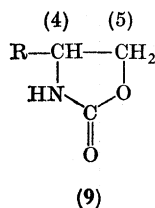
Addition of INCO to terminal olefins results in Markovnikoff addition and leads to 4-alkyl-2-oxazolidones (equation (9)). Addition of DCU

$$
\text{R—CH=CH}_2 \xrightarrow[\text{2. CH}_3\text{OH}]{\text{1. INCO}} \underset{\text{NHCOOCH}_3}{\text{R—CH—CH}_2\text{I}} \xrightarrow{\Delta} \text{R—CH—CH}_2 \qquad (9)
$$

(9)
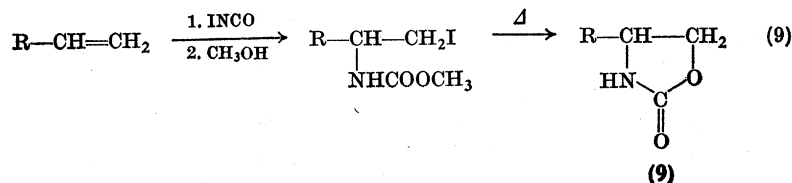
to terminal olefins occurs in anti-Markovnikoff fashion, and 5-alkyl-2-oxazolidones are obtained by pyrolysis (equation (10)).

$$
\text{R—CH=CH}_2 \xrightarrow{\text{DCU}} \underset{\text{Cl} \quad \text{NHCOOC}_2\text{H}_5}{\text{R—CH—CH}_2} \xrightarrow{\Delta} \text{R—CH—CH}_2 \qquad (10)
$$

(10)

β-Halocarbamates formed from internal olefins undergo pyrolysis to give 4,5-dialkyl-2-oxazolidones (11), but here the additional problem of stereochemistry arises. A study of the pyrolytic cyclisation of

$$
\underset{\displaystyle \underset{\text{O}}{\parallel}}{\underset{\text{HN}\diagdown\underset{\text{C}}{}\diagup\text{O}}{\text{R—CH—CH—R'}}}
$$

(11)
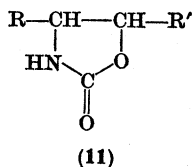
the *threo* and *erythro* β-iodocarbamates from *cis*- and *trans*-but-2-ene and from *cis*- and *trans*-hex-3-ene has shown (Foglia and Swern, 1969) that the reaction is stereoselective, not stereospecific. The pyrolysis of the corresponding β-chlorocarbamates has not yet been studied.

A series of long-chain alkyl substituted 2-oxazolidones prepared by Dyen and Swern (1968) is listed in Table 2. A comprehensive review of the chemistry of these compounds (Dyen and Swern, 1967) indicates
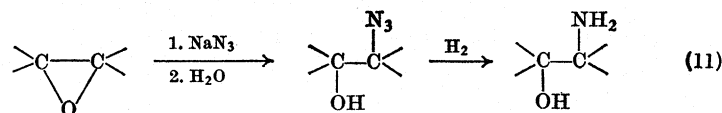
TABLE 2

$$R'\text{---}CH\text{---}CH\text{---}R$$

Long-chain aliphatic 2-oxazolidones

R	R′	Isomer	mp, °C
$CH_3(CH_2)_7$	$(CH_2)_7CH_3$	*cis*	15·0–16·0
$CH_3(CH_2)_7$	$(CH_2)_7CH_3$	*trans*	22·5–23·5
$CH_3(CH_2)_7$ $CH_3OOC(CH_2)_7$	$(CH_2)_7COOCH_3$ $(CH_2)_7CH_3$	*cis*	Oil
$CH_3(CH_2)_7$ $CH_3OOC(CH_2)_7$	$(CH_2)_7COOCH_3$ $(CH_2)_7CH_3$	*trans*	Oil
$CH_3(CH_2)_7$ $HOCH_2(CH_2)_7$	$(CH_2)_7CH_2OH$ $(CH_2)_7CH_3$	*trans*	Oil
$CH_3(CH_2)_9$	H	—	31·5–32·5
$CH_3(CH_2)_{11}$	H	—	46·0–47·0
$CH_3(CH_2)_{13}$	H	—	54·0–55·0

[1] Dyen and Swern (1968).

that they may be interesting intermediates in the synthesis of various fatty acid derivatives, such as vicinal aminohydroxy acids. The latter, however are more readily available by other synthetic procedures such as the addition of azides to epoxides (equation (11)).

$$\underset{O}{>C\text{---}C<} \xrightarrow[\text{2. H}_2\text{O}]{\text{1. NaN}_3} \underset{OH}{>C\text{---}\overset{N_3}{C}<} \xrightarrow{H_2} \underset{OH}{>C\text{---}\overset{NH_2}{C}<} \qquad (11)$$

Iodine isocyanate and dichlorourethane are only two of the several pseudohalogens whose addition of olefins has been studied, however, these two reagents have been examined in considerably greater depth than most of the others. It is perhaps for this reason that INCO and DCU seem to offer greater immediate opportunities for the synthesis of chain-substituted aliphatic nitrogen compounds, especially aziridines, than some of the other reagents which follow.

The addition of chlorine azide (ClN_3) and bromine azide (BrN_3) to the double bond of 3-keto-Δ^4-steroids has been reported (Drefahl, Ponsold, and Eichhorn, 1968). These pseudohalogens were prepared by addition of a solution of N-halogensuccinimide in t-butyl alcohol

to a solution of olefin and hydrazoic acid in chloroform. After reduction of the keto function, the β-haloazide of proper stereochemistry was easily reduced to the corresponding aziridine (equation (12)). The

X = Br or Cl

(12)
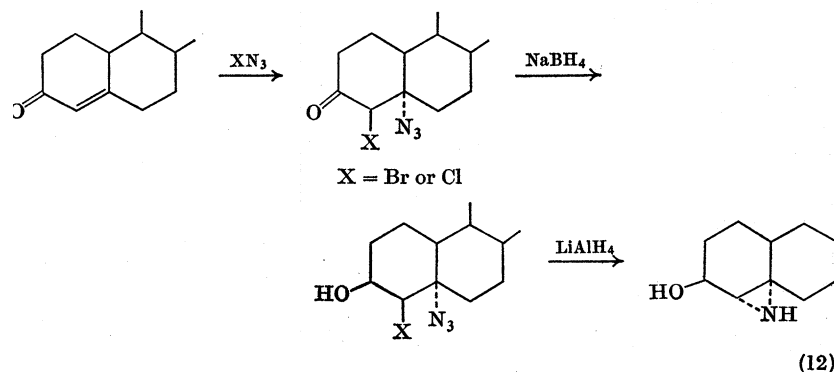
addition of bromine azide to *cis*- and *trans*-but-2-ene (Hassner and Boerwinkle, 1968) is stereospecific when carried out under ionic conditions, but yields are rather low. Iodine azide, prepared from iodine monochloride and sodium azide in acetonitrile, also adds stereospecifically to *cis*- and *trans*-but-2-ene and to other internal and terminal olefins as well (Fowler, Hassner, and Levy, 1967; Hassner and Fowler, 1968), and the β-iodoazides so formed can be isolated in up to 90 per cent yields. The adducts are quite labile to base and are readily converted to substituted vinyl azides (equation (13)) The latter can then be transformed into azirines. The halogen azides have

trans

(13)

(14)
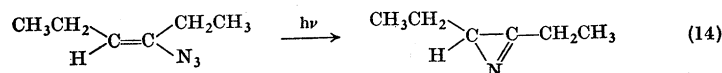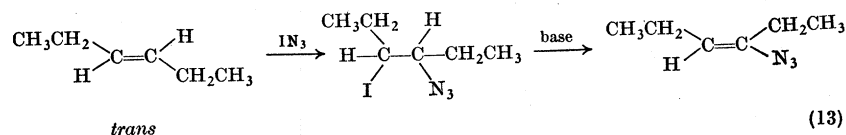
all been reported to be explosive when pure, and they should be handled with caution. Their preparation in solution seems to present no particular problems, but their reactions with certain olefins, particularly those containing sulphur, have been described as being violent. As yet the reactions of halogen azides with long-chain internal
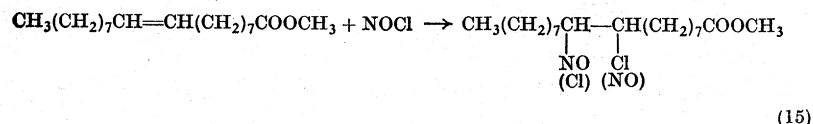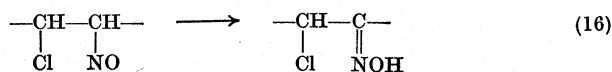
olefins have not been reported, but such reactions appear to offer considerable promise.

The reaction of nitrosyl chloride with olefins has been known for almost 100 years (Tilden and Shenstone, 1877), and an extensive wealth of literature has accumulated on this subject. Comprehensive literature reviews (Beckham, Fessler, and Kise, 1951; Kadzyauskas and Zefirov, 1968) have summarised the present state of knowledge, and it is necessary here only to highlight the application of this reaction to fatty acid chemistry. It was shown some time ago (Tilden and Forster, 1894) that nitrosyl chloride adds to oleic and elaidic acids quite readily, but there is some doubt regarding the nature of the products isolated at that time. About 30 years ago (Kaufmann and Röver, 1940) the reaction was utilised in an analytical method to determine the amount of unsaturation in fats and was shown to give about the same results as the iodine monochloride method. However, only the disappearance of NOCl was measured, and no attempts were made to isolate products.

Re-examination has demonstrated (Miller, Pryde, Cowan, and Teeter, 1965) that the addition of nitrosyl chloride to methyl oleate is essentially quantitative, when the reaction is carried out at 2° and the solvent is methylene chloride. The product, methyl 9(10)-chloro-10(9)-nitrosostearate, is formed according to equation (15). The di-

$$CH_3(CH_2)_7CH\!=\!CH(CH_2)_7COOCH_3 + NOCl \longrightarrow CH_3(CH_2)_7\underset{\underset{(Cl)}{\overset{NO}{|}}}{CH}\!-\!\underset{\underset{(NO)}{\overset{Cl}{|}}}{CH}(CH_2)_7COOCH_3$$

(15)

meric product which is so often observed in the reactions of nitrosyl chloride with olefins is not formed in significant amounts under these conditions. The usually facile rearrangement of the secondary nitroso compound to the oxime (equation (16)) proceeds slowly on standing

$$-\underset{\underset{Cl}{\overset{|}{|}}}{CH}\!-\!\underset{\underset{NO}{\overset{|}{|}}}{CH}\!- \longrightarrow -\underset{\underset{Cl}{\overset{|}{|}}}{CH}\!-\!\underset{\underset{NOH}{\overset{\|}{}}}{C}\!-$$ (16)

and is not easily accelerated. The stereochemical course of the nitrosochlorination of methyl oleate has not been investigated, and the literature concerning the nitrosochlorination of other olefins does not provide a satisfactory guide. The addition of NOCl and NOBr to norbornene derivatives follows a *cis* stereochemical course, but the nitrosochloride derived from Δ^9-octalin is *trans* (Meinwald, Meinwald,

and Baker, 1964). Furthermore, there is considerable evidence that the stereochemistry of nitrosochlorination depends not only on the structure of the alkene, but also on the solvent employed, the manner of preparation of the nitrosyl chloride, and on other factors.

Undoubtedly, the nitrosochlorination of unsaturated fatty acids and other long-chain aliphatic olefins will be investigated further, since it is potentially useful in the synthesis of fatty nitrogen derivatives. A superficial examination of some of the reactions of methyl chloro-nitrosostearate (Scheme II) has indicated that a variety of products can be prepared (Miller *et al.*, 1965) and has shown the value of this type of adduct as an intermediate. Not yet demonstrated, but certainly within the realm of reasonable possibility, is the conversion of fatty chloronitroso derivatives to the valuable aziridines (equation (17)). This transformation has been accomplished on nitrosochlorides

$$\underset{\underset{\text{Cl}\quad\text{NO}}{|\quad\ \ |}}{>\!\!C\!-\!C\!\!<} \quad\xrightarrow{\text{reduction}}\quad \underset{\underset{\text{Cl}\quad\text{NH}_2}{|\quad\ \ |}}{>\!\!C\!-\!C\!\!<} \quad\xrightarrow{\text{base}}\quad \underset{\underset{\text{H}}{\text{N}}}{>\!\!C\!-\!C\!\!<} \qquad (17)$$
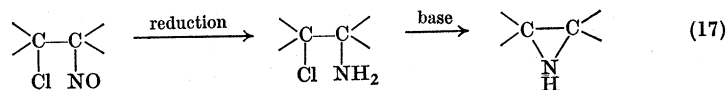
derived from tetra-alkylethylenes (Closs and Brois, 1960), but it failed in the attempted application to those derived from mono-, di-, and tri-alkylethylenes.
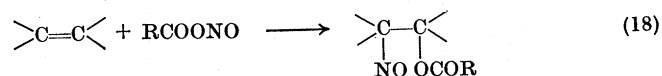
The reaction of nitrosyl acylates, especially nitrosyl formate, with olefins is analogous to nitrosochlorination (Hamann and Swern, 1968). Markovnikoff addition is the rule, and the stereochemistry is dependent on the olefin treated and on reaction variables. The reaction is illustrated in equation (18). *trans*-Hex-3-ene is the only aliphatic

$$>\!\!C\!=\!C\!\!< + \text{RCOONO} \quad\longrightarrow\quad \underset{\underset{\text{NO}\quad\text{OCOR}}{|\quad\ \ |}}{>\!\!C\!-\!C\!\!<} \qquad (18)$$

internal olefin which has been subjected to nitrosoformylation, and it gave poor yields of a mixture of nitroso and oximino formates. At the present time nitrosoformylation seems to present no advantages over the reactions of nitrosyl chloride, a reagent which is available commercially in acceptable purity.

Among the pseudohalogens whose addition to aliphatic olefins could, in theory at least, lead to aziridine precursors, are several, less common, nitrogen compounds. Nitryl iodide (Kropp, 1966), formed *in situ* from silver nitrite and iodine, and nitryl chloride (Price and Sears, 1953) add to olefins to form the respective β-nitrohalides, but

SCHEME II

$$
\text{R—CH—CH—R}' \quad
\begin{array}{c}
\text{C}_5\text{H}_{10}\text{NH} \\ \longrightarrow
\end{array}
\quad
\begin{array}{c}
\text{R—CH—CH—R}' \\ \;\;|\qquad| \\ \text{NO}\quad\text{NC}_5\text{H}_{10}
\end{array}
$$

R—CH—CH—R′
  | |
NO Cl

C₅H₁₀NH →
R—CH—CH—R′
  | |
NO NC₅H₁₀

CH₃ONa →
R—CH—CH—R′
  | |
NO OCH₃

KOH →
R—CH—CH—R′
  | |
NO OH

NH₃ →
R—CH—CH—R′
  | |
NO NH₃

AcONa, DMSO →
R—CH—CH—R′
  | |
NO OAc

(C₂H₅)₃N →
R—C=CH—R′
  |
NO

Zn, AcOH →
R—CH—CH—R′
HONH Cl

R = CH₃(CH₂)₇

R′ = (CH₂)₇COOCH₃
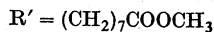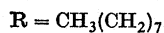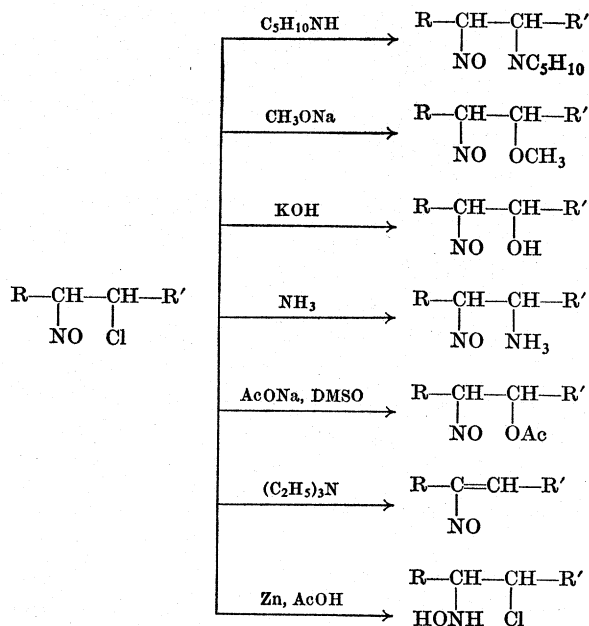
yields are low. On the other hand, iodine nitrate, from silver nitrate and iodine, forms only β-iodonitrates.

The preparation and purification of monochlorourethane (MCU) (Saika and Swern, 1968) is more difficult and tedious than that of dichlorourethane (DCU), and therefore the latter is preferred in the preparation of aziridines. However, MCU adds photochemically to olefins (Schrage, 1966, 1967) in a manner which is entirely analogous to that of DCU and therefore leads to the same products. Similarly, N,N-dichloro-N',N'-dimethylsulphamide (**12**) and O,O-diethyl-N,N-dichlorophosphoramidate (**13**) add to olefins in a free radical manner (Greatbanks, Seden, and Turner, 1968; Zwierzak and Koziara, 1968) to give β-chloroamine derivatives (equation (19)). The addition product of (**12**) and styrene has been cyclised to form the substituted aziridine (equation (20)). The addition of N,N-dibromo- and N,N-dichloroarylsulphonamides to olefins has been investigated extensively. The mode of addition, free radical or ionic, seems to depend

$$\underset{R}{\overset{H}{}}C{=}C\underset{R'}{\overset{H}{}} + \text{YNCl}_2 \longrightarrow \underset{R}{\overset{Cl}{\underset{|}{\overset{|}{H-C}}}}\underset{R'}{\overset{N-Cl}{\underset{|}{\overset{|}{-C-H}}}} \qquad (19)$$

NaHSO₃

$$\underset{R}{\overset{Cl}{\underset{|}{\overset{|}{H-C}}}}\underset{R'}{\overset{\overset{Y}{\underset{|}{N-H}}}{\underset{|}{-C-H}}}$$

12 Y = (CH₃)₂NSO₂—
13 Y = (C₂H₅O)₂PO—
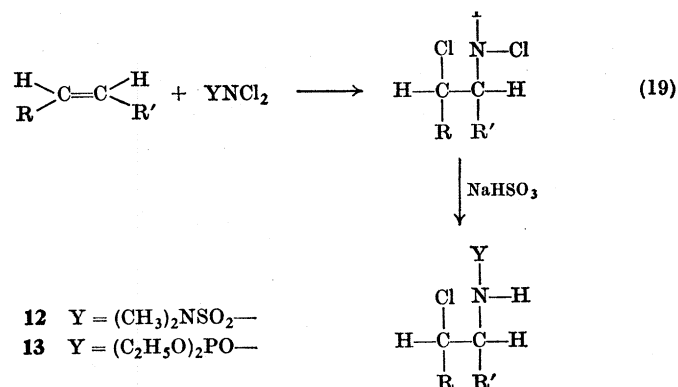
on the reagents used and on the conditions employed. Treatment of a series of aliphatic internal olefins in carbon tetrachloride with N,N-dibromobenzenesulphonamides (Foglia, Haeberer, and Maerker,

$$\underset{C_6H_5}{\overset{Cl}{\underset{|}{\overset{|}{H-C}}}}\underset{H}{\overset{NHSO_2N(CH_3)_2}{\underset{|}{\overset{|}{-C-H}}}} \overset{OH^-}{\longrightarrow} \underset{C_6H_5}{\overset{H}{}}C\overset{\overset{SO_2N(CH_3)_2}{N}}{\diagup \diagdown}CH_2 \qquad (20)$$
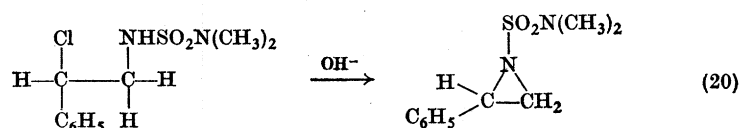
1970a) followed by reduction with bisulphite gives β-bromoalkyl-benzenesulphonamides resulting from an ionic, stereoselective addition. Conversion of the adducts to substituted aziridines is effected with base (Tables 3 and 4).

(ii) *From olefins via nitrenes.* The most direct conceivable synthetic route from olefins to aziridines involves the addition of the electron deficient species NH to the double bond (equation (21)). This

$$R{-}CH{=}CH{-}R + \overset{..}{\underset{..}{N}}H \longrightarrow R{-}CH{\overset{\overset{H}{N}}{\diagup \diagdown}}CH{-}R \qquad (21)$$
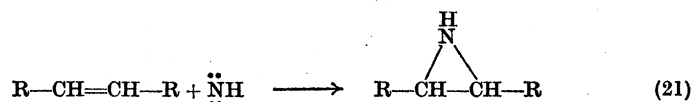
reaction has not yet been achieved on a practical basis, but related reactions have, and these are the subject of the brief survey comprising this section.

Monovalent, electron-deficient nitrogen intermediates which have no electrical charge are commonly known as nitrenes, although other names such as imidogens, imines, and azenes are found in the literature. The name nitrene is preferred by most authors because of the chemical similarity of these species to the well-known carbenes. The preparation

and properties of nitrenes have been studied extensively (Abramovitch and Davis, 1964; Horner and Christmann, 1963), but the state of knowledge does not approach that of the chemistry of carbenes.
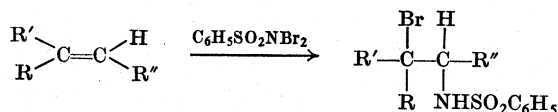
In general, nitrenes are prepared by the thermal or photolytic decomposition of azides or by base-induced α-elimination from a suitable species. Nitrenes can exist in two electronically distinct states: the singlet state in which the species has two sets of paired, unshared electrons and an unoccupied orbital; and the triplet state in which

TABLE 3

Addition of N,N-dibromobenzene sulphonamides to olefins[1]

$$R' \atop R \bigg\rangle C{=}C \bigg\langle {H \atop R''} \quad \xrightarrow{C_6H_5SO_2NBr_2} \quad R'{-}\underset{\underset{R}{|}}{\overset{\overset{Br}{|}}{C}}{-}\underset{\underset{NHSO_2C_6H_5}{|}}{\overset{\overset{H}{|}}{C}}{-}R''$$

| R | R′ | R″ | Configuration | | Pure product yield, % |
			Olefin	Product	
C_2H_5	H	C_2H_5	*cis*	*threo*	65
H	C_2H_5	C_2H_5	*trans*	*erythro*	52
C_4H_9	H	CH_3	*cis*	*threo*	65
C_4H_9	H	C_4H_9	*cis*	*threo*	60
C_8H_{17}	H	C_8H_{17}	*cis*	*threo*	42
H	C_8H_{17}	C_8H_{17}	*trans*	*erythro*	38
C_8H_{17}	H	$(CH_2)_7COOCH_3$	*cis*	*threo*	60

[1] Foglia, Haeberer, and Maerker (1970a).

one orbital is occupied by a pair of unshared electrons and two orbitals each contain one electron, and the spin of the single electrons is parallel. The principal productive reactions of nitrenes are additions to double bonds and insertions, principally in carbon–hydrogen bonds. These reactions occur competitively when a nitrene is contacted with an olefin, particularly an aliphatic one, and it is this competition which concerns the 'oleochemist'.

Ethoxycarbonylnitrene (carboethoxynitrene) is probably the best known (Lwowski, 1967) of the electron-deficient nitrogen inter-mediates, although the reactions of many others have been reported. These include methanesulphonylnitrene (Abramovitch and Uma,

1968), arylsulphonylnitrenes (Breslow and Sloan, 1968; Breslow, Sloan, Newburg, and Renfrow, 1969), vinylnitrenes (Boyer, Krueger, and Mikol, 1967), cyanonitrene (Anastassiou and Simmons, 1967), aryl nitrenes (Smolinsky and Feuer, 1964), fluoronitrene (leNoble and Skulnick, 1967), NH (Cornell, Berry, and Lwowski, 1960) and others. As expected, the covalently bound group influences the behaviour and

TABLE 4

Formation of aziridines from β-bromoalkylbenzenesulphonamides[1]

			Configuration		Yield of pure B, %
R	R'	R''	A	B	
C_2H_5	H	C_2H_5	*threo*	*cis*	75
H	C_2H_5	C_2H_5	*erythro*	*trans*	80
C_4H_9	H	CH_3	*threo*	*cis*	75
C_4H_9	H	C_4H_9	*threo*	*cis*	75
C_8H_{17}	H	C_8H_{17}	*threo*	*cis*	80
H	C_8H_{17}	C_8H_{17}	*erythro*	*trans*	65
C_8H_{17}	H	$(CH_2)_7COOCH_3$	*threo*	*cis*	70

[1] Foglia, Haeberer, and Maerker (1970a).

modifies the properties of the electron-deficient nitrogen to some extent, but qualitatively the reactions of the various nitrenes are similar. Ethoxycarbonylnitrene will serve to illustrate the behaviour of this group of reactive intermediates.

Ethoxycarbonylnitrene (14) can be prepared by the photolytic or thermal decomposition (Lwowski and Mattingly, 1965) of ethyl azido-formate (equation (22)) or by the base-catalysed cleavage (Lwowski

(22)
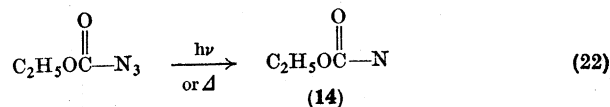
and Maricich, 1965) of N-(p-nitrobenzenesulphonyloxy)urethane (15) as shown in equation (23). Nitrene (14), generated by any of the three

$$C_2H_5O\overset{\overset{O}{\|}}{C}\text{—NH—O—SO}_2\text{—}C_6H_4\text{—}NO_2 + B: \longrightarrow$$
(15)

$$C_2H_5O\overset{\overset{O}{\|}}{C}\text{—N} + O_2NC_6H_4SO_3^- + \overset{+}{B}H \quad (23)$$
(14)
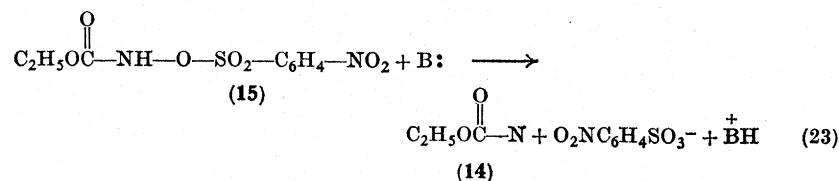
methods, inserts in the C—H bonds of 2-methylbutane as shown in equation (24). The order of reactivity of C—H bonds is $3^0 > 2^0 > 1^0$ and the magnitudes of the relative amounts of products formed are

$$\begin{array}{c} H_3C \quad CH_3 \\ \diagdown \diagup \\ CH \\ | \\ CH_2 \\ | \\ CH_3 \end{array} \quad + \quad (14) \qquad\qquad (24)$$

↓

$$\begin{array}{c} H_3C \quad CH_3 \\ \diagdown \diagup \\ \underset{\|}{\overset{}{C}}\text{—NHCOC}_2H_5 \\ | \quad O \\ CH_2 \\ | \\ CH_3 \end{array} + \begin{array}{c} H_3C \quad CH_3 \\ \diagdown \diagup \\ CH \quad O \\ | \quad \| \\ CHNHCOC_2H_5 \\ | \\ CH_3 \end{array} + \begin{array}{c} \quad\quad\quad O \\ \quad\quad\quad \| \\ H_3C \quad CH_2NHCOC_2H_5 \\ \diagdown \diagup \\ CH \\ | \\ CH_2 \\ | \\ CH_3 \end{array} + \begin{array}{c} H_3C \quad CH_3 \\ \diagdown \diagup \\ CH \\ | \quad O \\ CH_2 \quad \| \\ CH_2NHCOC_2H \end{array}$$

(16)   (17)   (18)   (19)
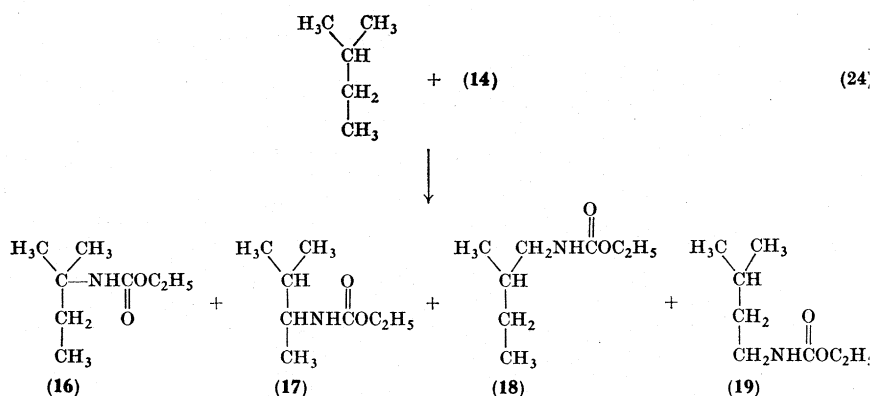
qualitatively the same regardless of the method of generation of (14). There is about 30 times as much tertiary product (16) formed as primary (18 + 19), although the ratio of primary hydrogens to tertiary is 9 : 1.

The reaction of carbethoxynitrene (14) which is of greater interest than insertion, in the framework of the present discussion, is its ability to add to double bonds to form aziridines. This reaction has not yet been applied to long-chain fatty esters, such as methyl oleate, although it probably will be in the near future. Yields as high as 78 per cent have been achieved (Lwowski, 1967) in the addition of (14), produced by thermolysis, to 4-methylpent-2-ene. This indicates that addition to double bonds is considerably faster than insertion. Experimentally it has been found (Lwowski and Woerner, 1965) that in the addition of (14) to cyclohexene the ratio of aziridines to insertion

products varies from 3:1 at high concentration to 20:1 at low concentration of olefin.

The stereochemistry of the formation of aziridines by nitrene addition to olefins is particularly relevant. The addition of nitrene (14) to both cis- and trans-4-methylpent-2-ene is stereoselective, and the predominent species of aziridine formed has the same geometry as the starting olefin (McConaghy and Lwowski, 1967). Similar results have been obtained in the addition of methoxycarbonyl nitrene to cis- and trans-but-2-ene (Hafner, Kaiser, and Puttner, 1964). It is believed that singlet nitrenes add stereospecifically to olefins and that triplet nitrenes, on the other hand, give a mixture of two geometrically isomeric aziridines. Addition of triplet nitrene is visualised to proceed in two steps, the first of which gives rise to a diradical which can rotate. The stereochemistry of ring closure is therefore determined by the relative stabilities of the conformations of the diradical. Ethoxycarbonylnitrene generated by thermolysis of the azide or by α-elimination is believed to be pure s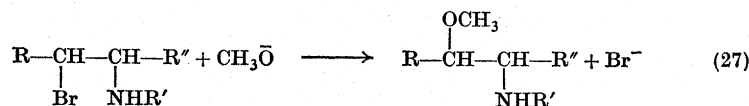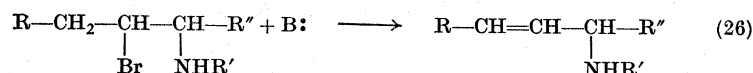inglet, but it partially inverts to triplet before addition to the double bond. Photolytically produced (14), on the other hand, is a mixture of singlet and triplet nitrene. Experimental evidence (Smolinsky and Feuer, 1964; Lwowski and Johnson, 1967) further indicates that only singlet nitrene undergoes C—H insertion and that triplet nitrene does not.

The present knowledge of nitrene chemistry can be projected to the desired preparation of epimino derivatives of long-chain aliphatic compounds by nitrene addition. Since C_{18} mono-olefins, such as methyl oleate, contain only one double bond but 28 secondary C—H bonds, it would be expected that singlet nitrene will give poor yields of aziridines because of the high probability of insertion. Triplet nitrene addition may be more successful in this case, but aziridine yields may be decreased somewhat by hydrogen abstraction. The aziridines formed by triplet addition will, of course, be a mixture of stereoisomers. Furthermore an efficient method for converting singlet into triplet nitrene is necessary before such a process can become practical. This, however, is no great obstacle, and practical one-step synthesis of aziridines from derivatives of fats do not seem far in the future.

(iii) *By miscellaneous syntheses.* Historically, ethylenimine (aziridine) (1) was first prepared by Gabriel (1888) by the action of base on 2-bromoethylamine (equation (25)). The name Gabriel synthesis is now a concept applied generally to the base catalysed cyclisation of β-haloamines and represents the most commonly used procedure

$$\underset{\substack{| \\ \text{Br} \quad \text{NH}_2}}{\text{CH}_2\text{---CH}_2} + \text{KOH} \longrightarrow \underset{\substack{\diagdown \ \diagup \\ \underset{\text{H}}{\text{N}}}}{\text{CH}_2\text{---CH}_2} + \text{KBr} + \text{H}_2\text{O} \tag{25}$$
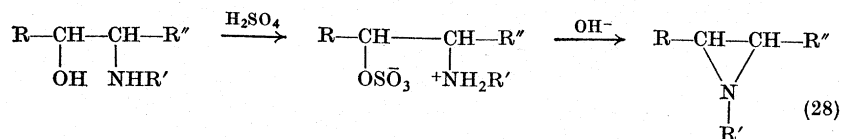
$$(1)$$
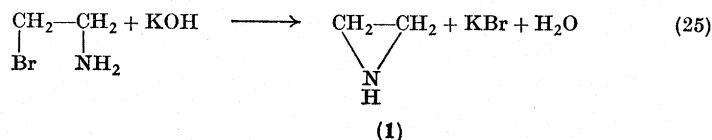
in the preparation of unsubstituted or substituted aziridines. In the strictest sense, all the syntheses of aziridines by way of pseudohalogen addition to olefins include, as their final step, a Gabriel synthesis cyclisation. Numerous examples of this procedure have been reported in the literature and are cited in review articles dealing with aziridine syntheses. Side reactions which are sometimes encountered in the employment of this method are elimination of hydrogen halide without cyclisation (equation (26)) and nucleophilic displacement of halogen (equation (27)). The synthetic route is not easily applicable to the

$$\underset{\substack{| \quad | \\ \text{Br} \quad \text{NHR}'}}{\text{R---CH}_2\text{---CH---CH---R}''} + \text{B:} \longrightarrow \underset{\substack{| \\ \text{NHR}'}}{\text{R---CH=CH---CH---R}''} \tag{26}$$

$$\underset{\substack{| \quad | \\ \text{Br} \quad \text{NHR}'}}{\text{R---CH---CH---R}''} + \text{CH}_3\bar{\text{O}} \longrightarrow \underset{\substack{| \\ \text{NHR}'}}{\overset{\overset{\text{OCH}_3}{|}}{\text{R---CH---CH---R}''}} + \text{Br}^- \tag{27}$$

preparation of long-chain internal aziridines, since the β-haloamines required are themselves difficult to obtain except by the pseudohalogen addition route.

The Wenker reaction (Wenker, 1935) (equation (28)) is a modifica-

$$\underset{\substack{| \quad | \\ \text{OH} \quad \text{NHR}'}}{\text{R---CH---CH---R}''} \xrightarrow{\text{H}_2\text{SO}_4} \underset{\substack{| \quad | \\ \text{O}\bar{\text{S}}\text{O}_3 \quad {}^+\text{NH}_2\text{R}'}}{\text{R---CH------CH---R}''} \xrightarrow{\text{OH}^-} \underset{\substack{\diagdown \ \diagup \\ \underset{\text{R}'}{\text{N}}}}{\text{R---CH---CH---R}''} \tag{28}$$

tion of the Gabriel synthesis. β-Aminoalcohols are treated with sulphuric acid and the resulting sulphates are then heated with base. Undesirable side reactions are acid catalysed dehydration and retropinacol rearrangements, and these occur principally when the amino alcohols are highly branched. The Wenker reaction proceeds with inversion except when the hydroxyl group is attached to tertiary or benzylic carbon atoms. Use of the Wenkler reaction to prepare fat-derived aziridines has not been reported. The required β-amino alcohol precursors can be prepared by reactions of amines or azides with epoxides, but the overall synthetic route is not attractive.

The addition of carbenes to anils (equation (29)) leads to aziridines

(Cook and Fields, 1962), but the reaction is mentioned here only in passing since it is likely to find little application in the field of lipids.

It has been reported that aziridines can be formed in good yield upon treatment of ketoximes with lithium aluminium hydride (Kotera, Miyazaki, Takahashi, Okada, and Kitahonoki, 1968) or with Grignard

$$\text{C}_6\text{H}_4\text{—CH=N—C}_6\text{H}_4\text{—X} + :CCl_2 \longrightarrow \text{C}_6\text{H}_4\text{—CH—N—C}_6\text{H}_4\text{—X} \quad (29)$$
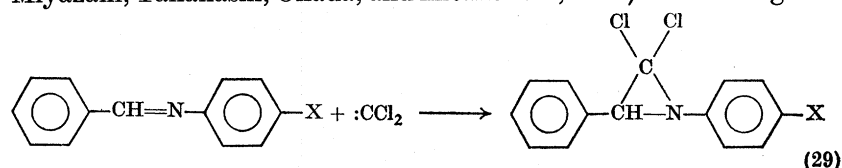
reagents (Laurent and Muller, 1969). These reactions have not yet been applied to strictly aliphatic systems, and their possible use in lipid derivatives suffers from the difficulties in obtaining the required ketone precursors. Also of marginal interest here are aziridine syntheses based on the pyrolysis (Fanta, 1964) or photolysis (Scheiner, 1965, 1968, 1969) of 1,2,3-triazolines, the pyrolysis of oxazolidones (Dyen and Swern, 1967) or the reaction of ammonia with secondary chlorides (Dix, 1969).

(d) Chemical reactions

A detailed discussion of the chemistry of aziridines is clearly beyond the scope of this chapter. Excellent reviews of the subject (Fanta, 1964; Gembitskii *et al.*, 1966) have appeared in recent years. The present discussion will be restricted to an overall glance at the types of reactions which these small ring heterocyclic compounds undergo and to a view of the state of knowledge of the chemistry of fatty aziridines in the light of the more general knowledge concerning ethylenimines.

Similarly to other homocyclic and heterocyclic small-ring systems, the aziridine ring is a highly reactive species. Substituents on the three-membered ring greatly modify its reactivity, and to some extent they influence the course of reactions. Much is known of the reactions of ethylenimine itself and of aliphatic aziridines, i.e. ethylenimine having one or more alkyl substituents in the 2- and 3-position, but the principal emphasis of past work has been on compounds in which the epimino function has been located in a terminal position on the aliphatic chain. The long-chain internal aziridines, upon which our attention is focused, are unsubstituted on nitrogen and thus belong to the class of 2,3-dialkylethylenimines. With the exception of

2,3-dimethylethylenimine (2,3-epiminobutane) these compounds are relatively new, and their chemistry has not yet been examined in detail. There is some question of the extent to which the known reactions of terminal aliphatic aziridines may be extrapolated to the long-chain internal epiminoalkanes. Certainly in the closely related field of epoxide chemistry it is well known that terminal and internal aliphatic epoxides do not always behave in the same manner. For instance, propylene oxide and other terminal epoxides are readily

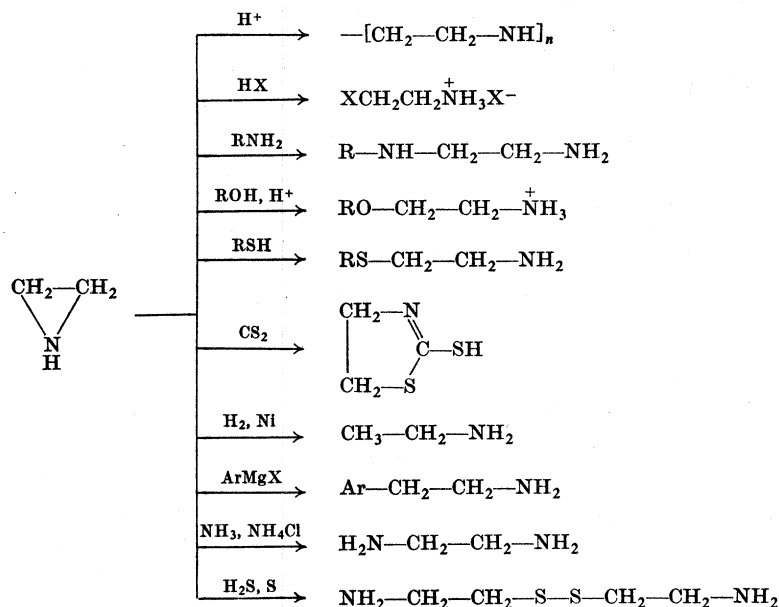SCHEME III. Ring preserving reactions of ethylenimine
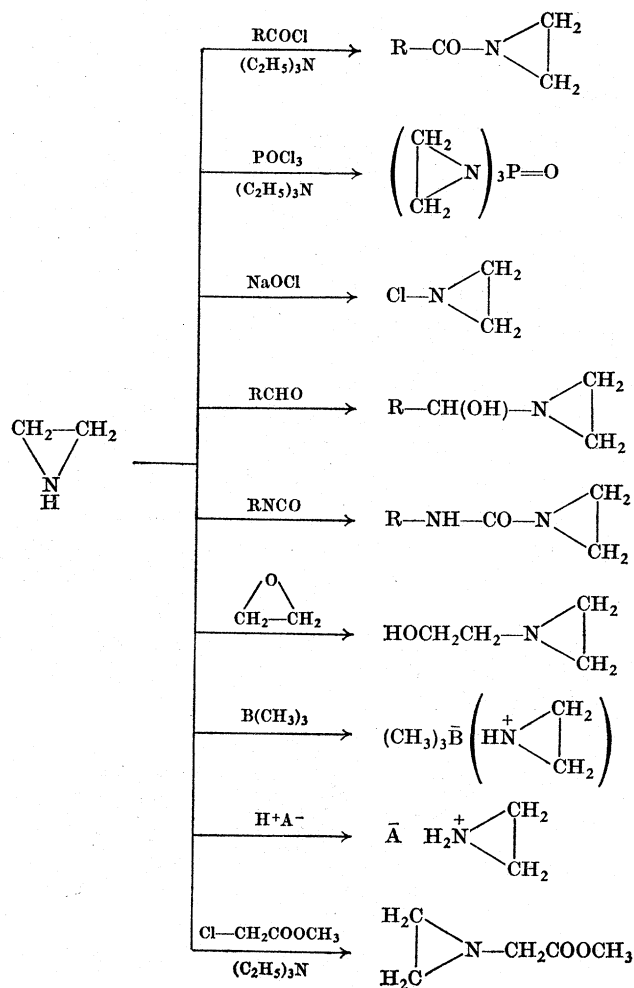
attacked by amines, hydroxide and other nucleophiles and bases, while 9,10-epoxyoctadecane is quite inert to such reagents.

Some typical reactions of ethylenimine are illustrated in Schemes III and IV. Two distinctly different modes of behaviour are apparent. In the reactions exemplified in Scheme III, aziridines behave as typical secondary amines and demonstrate the nucleophilicity and basicity of the nitrogen atom. On the other hand, the susceptibility of ethylenimines themselves toward nucleophilic attack results in the opening of the strained three-membered ring as shown in the reactions of Scheme IV. The tendency of ethylenimine to polymerise on contact

SCHEME IV. Ring opening reactions of ethylenimine.

$$\xrightarrow{\text{H}^+} \quad -[CH_2-CH_2-NH]_n$$

$$\xrightarrow{\text{HX}} \quad XCH_2CH_2\overset{+}{N}H_3X^-$$

$$\xrightarrow{\text{RNH}_2} \quad R-NH-CH_2-CH_2-NH_2$$

$$\xrightarrow{\text{ROH, H}^+} \quad RO-CH_2-CH_2-\overset{+}{N}H_3$$

$$\xrightarrow{\text{RSH}} \quad RS-CH_2-CH_2-NH_2$$

$$\xrightarrow{\text{CS}_2}$$

$$\xrightarrow{\text{H}_2, \text{Ni}} \quad CH_3-CH_2-NH_2$$

$$\xrightarrow{\text{ArMgX}} \quad Ar-CH_2-CH_2-NH_2$$

$$\xrightarrow{\text{NH}_3, \text{NH}_4\text{Cl}} \quad H_2N-CH_2-CH_2-NH_2$$

$$\xrightarrow{\text{H}_2\text{S, S}} \quad NH_2-CH_2-CH_2-S-S-CH_2-CH_2-NH_2$$

with acidic reagents is the result of nucleophilic attack of the free base on an aziridinium ion and thus reflects both types of behaviour by the heterocyclic compound. Ethylenimine and other aziridines are stable toward strong base except under forcing conditions, and their reactions with ammonia and amines are catalysed by water, alcohols or ammonium chloride. Acylated aziridines, on the other hand, are activated toward nucleophilic attack and react with amines without need of catalysts (Ham, 1964).
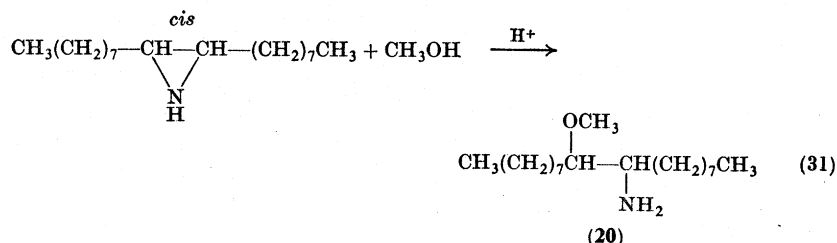
7

Rupture of a carbon–nitrogen bond of unsymmetrically substituted aziridines (equation (30)) can, and usually does, result in the formation

$$\text{R—CH—CH—R}' + \text{HY} \longrightarrow \text{R—CH—CH—R}' + \text{R—CH—CH—R}' \qquad (30)$$
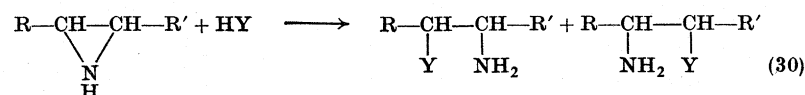
of two positional isomers. The relative amounts of the two products often vary and depend on the nature of the substituents R and R'.

Nucleophilic ring opening occurs with inversion at the carbon atom attacked (Hassner and Heathcock, 1963, 1965; Ponsold and Klemm, 1966) so that a *cis* aziridine gives rise to products having *threo* orientation and *trans* aziridines form *erythro* products. The rate of ring opening reactions of terminal alkyl aziridines depends largely upon the nucleophilicity of the attacking anion (Early, O'Rourke, Clapp, Edwards, and Lawes, 1958) and to a lesser extent on the alkyl substituent.

Long-chain internal aziridines, in contrast to ethylenimine and related terminal aziridines, show considerable stability towards acids in the absence of nucleophilic anions (Maerker, unpublished). For instance, excellent recoveries of *cis*-9,10-epiminooctadecane can be made after contact with fluoboric or sulphuric acids. On the other hand, the presence of even a weak nucleophile in acidic medium causes ring opening. For instance, methanol opens the aziridine ring in the presence of fluoboric acid or boron fluoride in accordance with equation (31). There is no evidence of polymerisation, and the amino-ether (20)

$$\text{CH}_3(\text{CH}_2)_7\text{—CH—CH—(CH}_2)_7\text{CH}_3 + \text{CH}_3\text{OH} \xrightarrow{\text{H}^+}$$

$$\text{CH}_3(\text{CH}_2)_7\overset{\text{OCH}_3}{\text{CH}}\text{—CH(CH}_2)_7\text{CH}_3 \qquad (31)$$

(20)

is isolated in high yield. Undoubtedly, protonation of the aziridine ring is the first step in this reaction.

A further illustration of the importance of anion nucleophilicity is provided by the reaction of halogen halides. Contact of 9,10-epiminooctadecane with hydrogen chloride, bromide, and iodide under similar conditions gives only about 8 per cent reaction with hydrogen chloride, but essentially quantitative addition with hydrogen iodide. The products are β-haloamines.
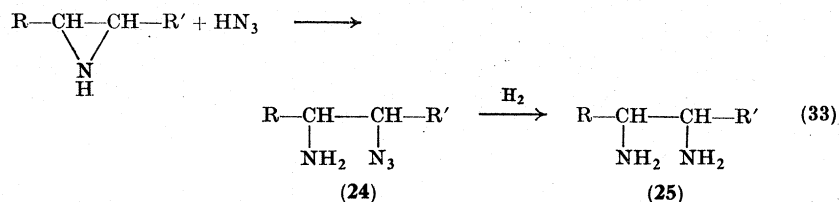
Although aziridines are weaker bases than the corresponding di-alkylamines (Fedor, Bruice, Kirk, and Meinwald, 1966) carboxylic acids are capable of catalysing the ring opening of aziridines. The reaction of acetic acid with ethylenimine (Jones, Zomlefer, and Hawkins, 1944) and with alicyclic derivatives (Hassner and Heath-cock, 1965; Ponsold and Klemm, 1966) occurs with inversion by nucleophilic attack of acetate. Acetic acid and other carboxylic acids also add to long-chain aliphatic internal aziridines (McGhie and Warren, 1968; Maerker, Haeberer, and Foglia, 1968; Maerker, Haeberer, Donahue, and Foglia, 1970). The reaction is shown as equation (32).

$$
\text{R—CH—CH—R'} + \text{R''COOH} \longrightarrow \left[\begin{array}{cc} \text{R—CH—CH—R'} & \text{R—CH—CH—R} \\ \underset{\text{NH}_2}{|} \quad \underset{\text{OCOR''}}{|} + \underset{\text{R''COO}}{|} \quad \underset{\text{NH}_2}{|} \end{array} \right]
$$

(21a)   (21b)   (32)

R—CH—CH—R'   R—CH—CH—R'   R—CH—CH—R'   R—CH—CH—R'
| | + | | + | | + | |
R'CONH OH   OH   NHCOR''   N   O   O   N
                                  \\   /   \\   //
                                   C   C
                                   | |
                                   R''   R''

(22a)   (22b)   (23a)   (23b)

The aminoesters (21) can be isolated when the reaction is carried out on short-chain terminal aziridines (Powers, Schatz, and Clapp, 1956) but the C_{18} internal aminoesters rearrange immediately to mixtures of hydroxyamides (22) and Δ^2-oxazolines (23). The relative amounts of oxazolines formed depend on the reaction conditions, the solvent employed, and the nature of the carboxylic acid. Hydroxy-amides are isolated in 70–90 per cent yields.

Acyl migrations such as (21) → (22), and the reverse migration (22) → (21), are quite common in organic chemistry. In the compounds in question the hydroxyamides (22) are the more stable species in neutral or alkaline media. Treatment of (22) with anhydrous hydro-chloric acid in dioxan (van Tamelen, 1951) results in conversion to the hydrochloride salt of (21). Contact of the latter with mild base such as sodium or lead acetate causes immediate reversion to the hydroxamide (22) (Maerker et al., 1970b).

Internal aliphatic aziridines resist attack by sodium azide alone, but in the presence of an equimolar (to azide) amount of ammonium chloride (Swift and Swern, 1967) the ring is opened to form β-azido-amines (**24**). The latter derivatives are also formed by the addition of hydrazoic acid (equation (33)) and are readily reduced to the corresponding diamines (**25**). The aziridine ring can also be ruptured

$$R\text{—}CH\text{—}CH\text{—}R' + HN_3 \longrightarrow$$
$$\underset{\underset{\displaystyle H}{\displaystyle N}}{\diagdown\diagup}$$

$$\underset{(24)}{R\text{—}\underset{NH_2}{\underset{|}{CH}}\text{—}\underset{N_3}{\underset{|}{CH}}\text{—}R'} \xrightarrow{\;H_2\;} \underset{(25)}{R\text{—}\underset{NH_2}{\underset{|}{CH}}\text{—}\underset{NH_2}{\underset{|}{CH}}\text{—}R'} \qquad (33)$$

by extending heating with concentrated ammonia using ethanol as solvent (Swift and Swern, 1966). By this method potassium *cis*-9,10-epimino-octadecanoate can be converted stereospecifically to a salt of the *threo*-9,10-diamine in 43 per cent yield (equation (34)). The same product (**26**), or the corresponding *erythro* compound, can also be

$$CH_3(CH_2)_7\underset{\underset{\displaystyle N}{}}{CH}\text{—}CH(CH_2)_7CO\overline{O}K^+ \xrightarrow[\text{2. HOAc}]{\text{1. NH}_3}$$
$$\overset{\displaystyle H}{\underset{}{N}}\diagdown$$

$$\underset{(26)}{CH_3(CH_2)_7\underset{\overset{|}{{}^+NH_3A\bar{c}}}{\overset{\overset{\displaystyle NH_2}{|}}{CH}}\text{—}CH(CH_2)_7COOH} \qquad (34)$$
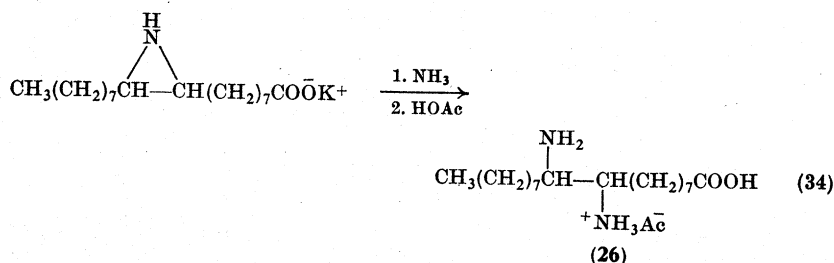
prepared stereospecifically from the 9,10-epoxide by a series of four steps involving two inversions. The azidohydroxyoctadecanoate formed by azide attack on the epoxide is converted to the azidomesyl-oxyoctadecanoate. The mesyloxy group is readily displaced by a second azide attack, and the diazidooctadecanoate is then reduced to the diamine. Each of the two azide groups causes inversion at the site of attack so that the *cis* epoxide gives rise to the *erythro* diamine and the *trans* epoxide to the *threo* diamine. The stereochemical assignments agree with those made in previous studies of reaction products of ammonia and amines with aziridines (Dickey, Fickett, and Lucas, 1952; Ghirardelli and Lucas, 1957).

Of the two available methods of converting aziridines to vicinal diamines, azide ring opening or reaction with ammonia, the former,
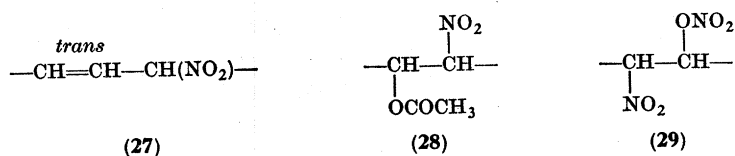
though longer, is preferred, since overall yields are higher and the reaction is cleaner.

3. Other Nitrogen Compounds

(a) Nitro, nitrato, and related derivatives

The direct substitution of hydrocarbons with nitric acid is successful only when conducted at high temperatures in the vapour phase; it then gives mixtures resulting from the replacement of all possible hydrogen atoms by nitro groups. Because of the low volatility of the most common fatty acids and their derivatives, and because of the lack of control over the location of substitution, this reaction is inherently unsuitable for the preparation of specific derivatives of fatty acids. On the other hand, the addition of nitric acid or of oxides of nitrogen to olefins has been studied under a variety of conditions, and nitro derivatives of fatty acids have been prepared by this route.
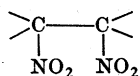
Treatment of oleic acid with concentrated nitric acid, first reported in the 1840's, is a chemical procedure which dates back to the very origins of synthetic organic chemistry. As practiced in early days, however, the reaction resulted in chain rupture and the production of non-nitrogenous mono- and di-carboxylic acids, principally suberic and azelaic acids. More recent studies indicate (Gut and Guyer, 1964) that the products obtained depend largely upon the reaction parameters (temperature, pressure, nitric acid concentration, etc.). Low temperature and dilute nitric acid favour the formation of nitro-nitrate addition products, but at higher temperature, higher pressure, or increased reaction time the primary products react further, and cleavage products predominate. If one carries out the nitration with acetyl nitrate (Malins and Houle, 1963; Houle and Malins, 1967) prepared *in situ* from nitric acid and acetic anhydride, one obtains three types of products from methyl oleate:

$$
\begin{array}{ccc}
trans & \overset{\displaystyle NO_2}{\underset{\displaystyle}{|}} & \overset{\displaystyle ONO_2}{\underset{\displaystyle}{|}} \\
-CH{=}CH{-}CH(NO_2){-} & -CH{-}CH{-} & -CH{-}CH{-} \\
 & \underset{\displaystyle OCOCH_3}{|} & \underset{\displaystyle NO_2}{|} \\
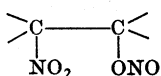(27) & (28) & (29)
\end{array}
$$

About 28 per cent of the nitration product is a mixture of nitro-olefins (27) in which more than one-half of the nitro groups are in the 8 and 11 positions, i.e. allylic to the original double bond, and all

double bonds are *trans*. This mixture of nitro compounds can be hydrogenated over Raney Nickel catalyst to a mixture of isomeric methyl aminostearates. Not unexpectedly, the nitration of methyl oleate with acetyl nitrate gives rise to considerable amounts (41 per cent) of acetoxy-nitro derivatives (28). These are undoubtedly mixtures of positional isomers, but their structures have not been determined. Nitro-nitrates (29) comprise about 23 per cent of the product mixture and they too, presumably, are mixtures of positional isomers. Products (28) and (29) are potential intermediates to amino alcohols. Alcohol derivatives of fatty acids, e.g. octadecanol, methyl 12-hydroxystearate, also react with acetyl nitrate, but in this case the products are nitrate esters (Malins, Wekell, and Houle, 1964).
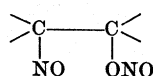
Oxides of nitrogen are often used, either alone or in conjunction with halogens, to nitrate olefins whose double bonds are either terminal, alicyclic, or are substituted with electron-withdrawing groups. Long-chain aliphatic compounds have been investigated only rarely and then superficially. The addition of pure dinitrogen tetroxide, or dinitrogen tetroxide in the presence of oxygen, to olefins is carried out at -10 to $25°$ in oxygen-containing solvents. The products are nitro-nitrates (29) dinitro compounds (30) or nitro-nitrites (31). In unsymmetrical olefins the nitro group usually appears at the carbon

$$\underset{\underset{NO_2}{|}}{>C}\!\!-\!\!\underset{\underset{NO_2}{|}}{C<} \qquad \underset{\underset{NO_2}{|}}{>C}\!\!-\!\!\underset{\underset{ONO}{|}}{C<} \qquad \underset{\underset{NO}{|}}{>C}\!\!-\!\!\underset{\underset{ONO}{|}}{C<}$$

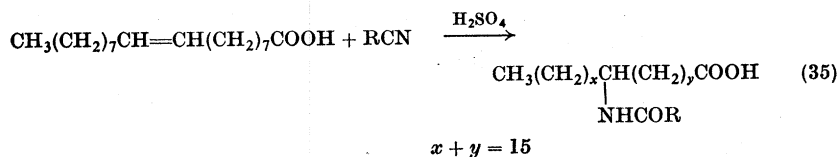$$\textbf{(30)} \qquad\qquad\qquad \textbf{(31)} \qquad\qquad\qquad \textbf{(32)}$$

bearing the most hydrogens (Schechter, 1964). Dinitrogen trioxide adds to olefins to give vicinal nitroso-nitrites (32) which are often dimeric (Park and Williams, 1969). The mechanisms of these additions are still incompletely understood and are subject to considerable controversy. The addition of nitrosyl halides to olefins has already been discussed in Section B.2(c) above. Vicinal nitrohalides are prepared by the addition of nitryl halides (Shvekhgeimer, Smirnyagin, Sadykov, and Novikov, 1968) or dinitrogen tetroxide and halogen (Stevens and Emmons, 1958; Bachman, Logan, Hill, and Standish, 1960) but applications of these reactions to fatty derivatives are still lacking.

(b) Amido derivatives

The acid-catalysed addition of nitriles to olefins, known as the Ritter reaction, has been utilised to synthesise nitrogen-substituted fatty

acids according to equation (35). Yields of secondary amides usually exceed 90 per cent (Roe and Swern, 1953), but the products are almost certainly mixtures in which the amide function is distributed over most of the carbon atoms of the chain, since it is well established

$$CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH + RCN \xrightarrow{\text{H}_2\text{SO}_4}$$

$$CH_3(CH_2)_x\underset{\underset{\text{NHCOR}}{|}}{C}H(CH_2)_yCOOH \qquad (35)$$

$$x + y = 15$$

(Showell, Swern, and Noble, 1968) that strong acid media cause carbonium ion migration along the fatty acid chain. When the R group of the nitrile is alkyl or aryl, the resulting mixture of secondary amides is difficult to hydrolyse to the corresponding amines. This difficulty is circumvented by using liquid hydrogen cyanide as the nitrile (Roe and Swern, 1955). The formamido derivatives, which result, are hydrolysed readily with 50 per cent sulphuric acid to form the amine, and the formic acid produced is separated by steam distillation. In another variation of the Ritter reaction (Thurston, 1955) the nitrile is a cyanogen halide and the amine can be obtained with minimum work-up. The Ritter reaction has been applied to a number of fatty acids including oleic, ricinoleic, hendecenoic, and petroselenic acid. Since oleic acid (octadec-9-enoic acid) and petroselenic acid (octadec-6-enoic acid) differ only in the location of the double bond, and since one would expect high mobility of the double bond in the strong sulphuric acid medium, it is anticipated that the two olefins give similar products. Nevertheless, although the addition of hydrogen cyanide to each acid proceeds in high yield, the pure product from oleic acid melts at 42–43° (Roe and Swern, 1955) and that from petroselenic acid melts at 82–85° (Holmes, Moreau, and Sumrell, 1965). It is difficult to attribute this lack of agreement to the slight difference in the reaction conditions employed.

The addition of acetonitrile to oleic acid in a modified Ritter reaction catalysed by hydrogen fluoride, rather than sulphuric acid, has been reported to proceed in 98 per cent yield (Potts, Miller, and Mais, 1967).

(c) Miscellaneous amino derivatives

The direct addition of ammonia to the double bonds of unsaturated fatty acids has not yet been accomplished on a practical basis. The

preparation of amino derivatives therefore requires detours via other reactive intermediates, and several such paths, such as ring-opening of aziridines and reduction of nitro derivatives, have been discussed in previous sections. A few additional routes will now be mentioned to complete the picture, but several of them have some serious disadvantages from the viewpoint of practicality.
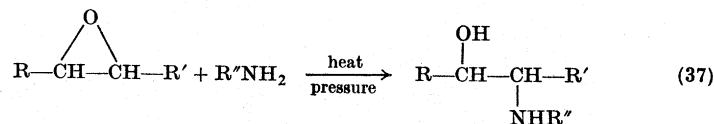
The ammonolysis of alcohols (equation (36)) is a common industrial vapour phase procedure which is applicable principally to the lower

$$ROH + NH_3 \rightarrow RNH_2 + H_2O \qquad (36)$$
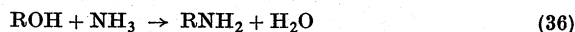
alcohols and to a limited extent to the higher primary alcohols. Hydroxy derivatives of fatty acid can be converted to the corresponding amines by oxidation to the ketones followed by oximination and reduction (Ismail and Simonis, 1963).

Nucleophilic displacement of halogen by ammonia or amines also leads to amines or substituted amines, but the reaction is practical for long-chain aliphatic halogen derivatives only if halogen is on a primary carbon atom or in an activated position, such as a carbon atom adjacent to a carboxy group. Secondary halogen compounds such as those obtained by halogenation or hydrohalogenation of an unsaturated fatty acid give poor aminolysis yields, because the basic nitrogen reagents cause considerable dehydrohalogenation.

Prior to the advent of fatty aziridines, the most convenient method of preparation for amino derivatives involved the ring-opening of epoxides with ammonia or amines. Since epoxides are rather resistant to nucleophilic attack in basic media, the reaction (equation (37)) is normally carried out at elevated temperature and pressure. This

$$ \overset{O}{\overset{\displaystyle\diagup\diagdown}{R\text{---}CH\text{---}CH\text{---}R'}} + R''NH_2 \xrightarrow[\text{pressure}]{\text{heat}} \underset{NHR''}{\overset{OH}{R\text{---}CH\text{---}CH\text{---}R'}} \qquad (37) $$

reaction has been utilised to prepare β-hydroxy amines from oleic acid (Swern and Findley, 1952), oleyl alcohol (Swern and Findley, 1948), oleonitrile (Rogier, 1960), oleamides (Rogier, 1964), petroselenic acid (Pigulevskii, Kuranova, and Sokolov, 1959), and others. The hydroxylamines can be converted to diamines by the method mentioned above (Swift and Swern, 1967), which involves treatment with methanesulphonyl chloride, displacement of the mesyloxy group with azides, and reduction of the latter.

C. SULPHUR COMPOUNDS

1. Introduction

This section is concerned with a discussion of fatty acid derivatives which have bivalent sulphur as a chain substituent and in which the sulphur is linked directly to carbon. Two well-known classes of sulphur-bearing lipid materials, the α-sulpho derivatives and the sulphate esters of fatty alcohols, are thus excluded from consideration.

Fatty materials substituted by bivalent sulphur find valuable applications in the lubricant and polymer fields. These products are usually prepared by the direct addition of sulphur or sulphur halides to the double bonds of unsaturated fats, but little is known concerning the structures of individual compounds.

Fatty episulphides have been known much longer than the corresponding nitrogen heterocycles, but the recent literature shows little evidence of activity either in the search for new methods of synthesis or in the investigation of the reactions of these sulphur compounds. This is somewhat surprising, since these heterocycles can be expected to be convenient intermediates to individual sulphur derivatives of fatty acids. Recent advances and innovations in sulphur chemistry would seem to provide the likelihood that fatty episulphides will eventually become available through photochemical synthesis, and that other sulphur-bearing entities will be derived from these reactive cyclic structures.

In this section the present state of knowledge of epithio fatty acids and other bivalent sulphur compounds is summarised.
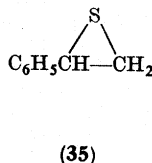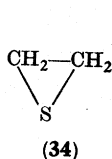
2. Episulphides

(a) Nomenclature

Episulphides are a class of compounds containing a three-membered saturated, heterocyclic ring in which the heterocyclic atom is bivalent sulphur. These structures are also sometimes known as olefin sulphides, thiiranes (compare oxiranes), and thiacyclopropanes. Although these names, particularly the latter two, are in accord with good nomenclature, they are not often used by organic chemists. For the purposes of this chapter, the term episulphide will be a general one describing this group of compounds, and the bivalent sulphur bridge between two adjacent, bonded carbon atoms will be designated as an 'epithio'

substituent. This is entirely in keeping with the naming of the corresponding nitrogen (epimino) and oxygen (epoxy) compounds explained in Section 2(a) above. Thus compound (33) will be named methyl 9,10-epithiostearate, for example. In keeping with common usage in the

$$CH_3-(CH_2)_7-CH-CH-(CH_2)_7COOCH_3$$
(33)
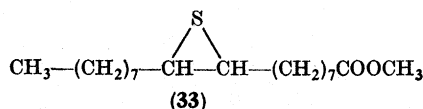
literature, however, simple episulphides will be named as olefin sulphides. Compound (34) is known as ethylene sulphide and (35) as styrene sulphide.

$$CH_2-CH_2$$
$$S$$
(34)

$$C_6H_5CH-CH_2$$
(35)

(b) Properties

The properties and reactions of episulphides have been summarised recently (Reynolds and Fields, 1964), but little information on fatty epithio derivatives was provided. Among the small-ring heterocyclic sulphur compounds, as in the nitrogen and oxygen series, the three-membered rings are less basic, i.e. have lower electron densities, than the 4–6 membered rings. This view is supported by ultraviolet (Davies, 1958) and NMR (Gutowsky, Rutledge, Tamres, and Searles, 1954) spectroscopic studies. The C_{18} or higher epithio fatty acids or alcohols are solids, the *trans* isomers melting higher than the *cis* while the corresponding esters are liquids or low melting solids (see Table 5).

Thin-layer chromatographic studies have been carried out on the separation of epithio and epoxy fatty acid derivatives with direct and reverse-phase TLC (Subbaram, Roomi, Achaya, 1966). The sulphur compounds are less polar by direct TLC than the corresponding oxygen derivatives, and the *trans* episulphides are less polar than the *cis* isomers. An increase in the distance of the epithio linkage from the carboxylate function decreases the polarity of the compounds as measured by direct TLC.

Ultraviolet absorption maxima at 257 mμ have been observed (Kaufmann and Schickel, 1963) for both *cis*-9,10-epithiostearic acid ($\epsilon = 52 \cdot 6$) and *cis,cis*-9,10,12,13-diepithiostearic acid ($\epsilon = 102 \cdot 6$). The

circular dichroism of the 9,10-epithiostearic acids has been measured and interpreted in terms of $n \rightarrow \sigma^*$ transitions (Bays, Cookson, Hill, McGhie, and Usher, 1964).
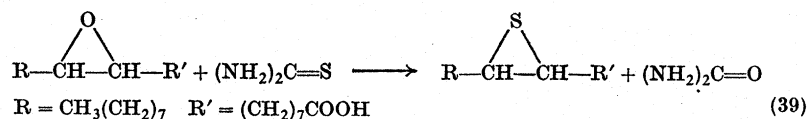
(c) Synthesis

Several different methods are available for the synthesis of aliphatic episulphides from the corresponding olefins. One of these involves the treatment of unsaturated compounds with a combination of sulphur and sulphur monochloride, followed by reduction of the resulting chloropolysulphides (Lautenschlaeger, 1968).

A more direct method of preparation of low molecular weight episulphides, and one which has great theoretical as well as practical interest, consists of the photochemical addition of atomic sulphur, to olefins (Strausz and Gunning, 1968). A mixture of singlet and triplet state sulphur atoms may be produced by ultraviolet photolysis of carbonyl sulphide (equation (38)) and reacts in the vapour state with

$$2COS + h\nu \rightarrow 2CO + S(^1D_2) + S(^3P) \tag{38}$$
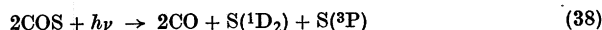
olefins to yield three types of products: episulphides, alkenyl mercaptans and vinylic mercaptans. In the presence of a large excess of carbon dioxide the concentration of singlet state sulphur, $S(^1D_2)$, is suppressed, no mercaptans are formed, and episulphides are generated in high yield. The reaction of $S(^3P)$ atoms, generated by COS photolysis in the presence of CO_2, with cis- and trans-but-2-ene gives 2,3-epithiobutane almost exclusively. Even more remarkably, the triplet atom addition is highly stereospecific, the specificity being over 95 per cent in the case of the cis isomer and over 99 per cent in the case of the trans isomer. Stereospecificity has previously been considered as indicative of the singlet spin state. Photochemical formation of episulphides from higher molecular weight olefins, particularly in condensed-phase reactions, remains to be studied.

Some of the most useful methods which are presently available for the preparation of internal, long-chain aliphatic episulphides depend on the reaction of epoxides with sulphur-containing reagents. Typical examples of the latter are thiocyanates, thiourea and substituted thioureas, thioamides, and xanthates. For instance, cis-9,10-epithiostearic acid can be prepared by treatment of cis-9,10-epoxystearic acid with thiourea (Kaufmann and Schickel, 1963) according to equation (39).

$$\underset{\substack{\diagup\diagdown}}{\overset{O}{}} \qquad \underset{\substack{\diagup\diagdown}}{\overset{S}{}}$$

R—CH—CH—R′ + (NH$_2$)$_2$C=S $\longrightarrow$ R—CH—CH—R′ + (NH$_2$)$_2$C=O

R = CH$_3$(CH$_2$)$_7$ R′ = (CH$_2$)$_7$COOH   (39)

A number of epithio-substituted fatty acids synthesised by this and similar methods are listed in Table 5.

The conversion of epoxides to episulphides occurs by a series of steps involving inversion at each of the carbon atoms of the epoxy

TABLE 5

Epithio derivatives of fatty acids
$$\underset{\substack{\diagup\diagdown \\ R—CH—CH—R'}}{\overset{S}{}}$$

R	R′	Isomer	mp °C	Reference[1]
CH$_3$(CH$_2$)$_{10}$	(CH$_2$)$_4$COOH	cis	74·5–75·5	a
CH$_3$(CH$_2$)$_{10}$	(CH$_2$)$_4$COOH	trans	78·0–79·0	a
CH$_3$(CH$_2$)$_7$	(CH$_2$)$_7$COOH	cis	58·0–58·5	a
			57·0–58·0	b
			60·0–62·0	c
CH$_3$(CH$_2$)$_7$	(CH$_2$)$_7$COOH	trans	63·0–64·0	a
			61·0–62·0	b
CH$_3$(CH$_2$)$_7$	(CH$_2$)$_{11}$COOH	cis	61·0–62·0	a
CH$_3$(CH$_2$)$_7$	(CH$_2$)$_{11}$COOH	trans	69·0–70·0	a
			71·0–73·5	c
CH$_3$(CH$_2$)$_7$	(CH$_2$)$_7$COOCH$_3$	cis	Oil, n_D^{20}1·4757	c
CH$_3$(CH$_2$)$_7$	(CH$_2$)$_{11}$COOCH$_3$	trans	33·0–35·0	c
$\overset{\overset{\textstyle S}{\diagup\diagdown}}{\text{CH}_3(\text{CH}_2)_4\text{—CH—CH—CH}_2}$ cis	(CH$_2$)$_7$COOH	cis	56·5	c
CH$_3$(CH$_2$)$_7$	(CH$_2$)$_7$CH$_2$OH	cis	49·5–50·5	c
CH$_3$(CH$_2$)$_7$	(CH$_2$)$_{11}$CH$_2$OH	cis	64·0	c
H	(CH$_2$)$_8$COOCH$_3$	—	Oil, bp 128–130/0·03 mm	c

[1] *Key to references.* (a) McGhie, Ross, Julietti, and Grimwood (1962). (b) Roomi, Subbaram, and Achaya (1967). (c) Kaufmann and Schickel (1963).

group. The reaction of cyclohexene oxide with thiocyanate takes place as shown in equation (40) (Van Tamelen, 1951).

Confirmation of this mechanism is found in the experimental conversion of D(+)-2,3-butene oxide to L(−)-2,3-butene sulphide with thiocyanate (Price and Kirk, 1953). The use of thiourea in place of thiocyanate in the conversion of epoxides to episulphides requires a

(40)
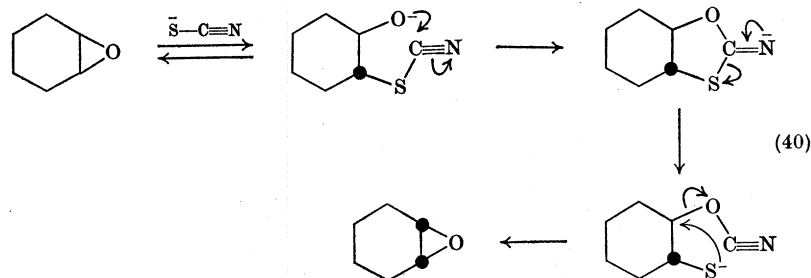
similar cyclic intermediate in the migration of carbon to sulphur (Bordwell and Andersen, 1953). Similar reaction paths have been demonstrated in episulphide syntheses using xanthates as source of

$$(H_2N)_2C=S + CH_2{-}CH{-}CH_3 \longrightarrow$$

(41)
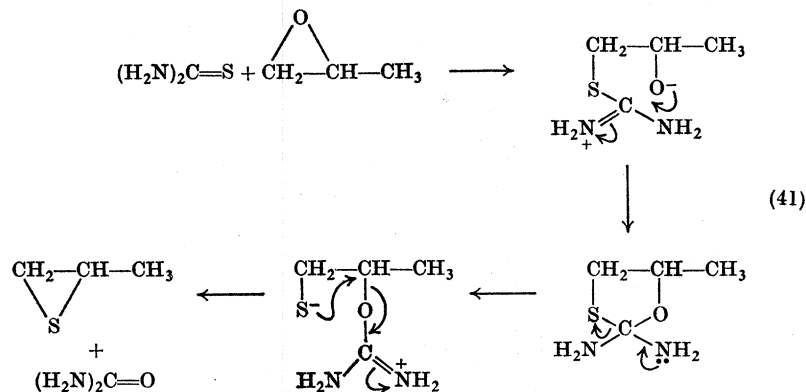
sulphur (Lightner and Djerassi, 1965; Overberger and Drucker, 1964).

Treatment of fatty acid epoxides with hydrogen sulphide in the presence of base (Umbach, Mehren, and Stein, 1969; Roomi, Subbaram, and Achaya, 1967) causes ring-opening in accordance with equation (42). When the mercaptohydroxides (36) are heated with

$$R{-}CH{-}CH{-}R' + H_2S \longrightarrow R{-}CH{-}CH{-}R' \qquad (42)$$

(36)

$$R = CH_3(CH_2)_7, \ R' = (CH_2)_7COOH$$
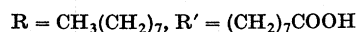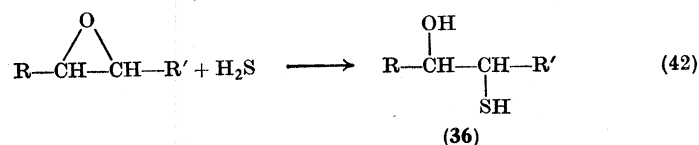
dry hydrogen chloride and then contacted with base, a mixture of epoxy- and epithio-octadecanoic acids is formed. Thus the indication is that anhydrous hydrogen chloride displaces either the hydroxy or the mercapto group (equation (43)).

$$(36) + 2HCl \longrightarrow \underset{\underset{Cl}{\overset{|}{}}\underset{SH}{\overset{|}{}}}{R-CH-CH-R'} \quad + \quad \underset{\overset{OH}{\overset{|}{}}\overset{Cl}{\overset{|}{}}}{R-CH-CH-R'}$$

<div align="center">↓ base   ↓ base   (43)</div>

$$\overset{\displaystyle S}{\overset{\diagup\diagdown}{R-CH-CH-R'}} \quad + \quad \overset{\displaystyle O}{\overset{\diagup\diagdown}{R-CH-CH-R'}}$$

$$R = CH_3(CH_2)_7 \quad R' = (CH_2)_7COOH$$
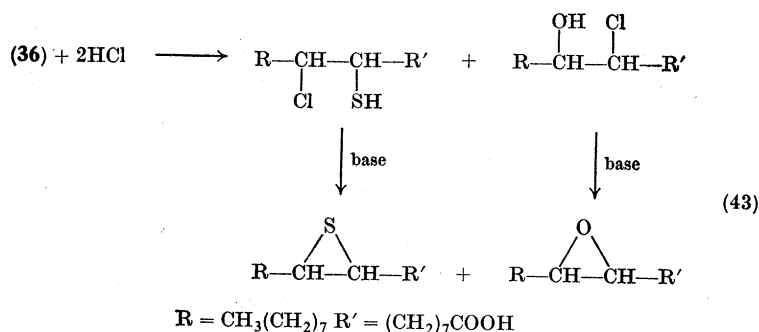
While it is often useful to employ epoxides as intermediates in the synthesis of epithio fatty acids, this intermediacy is not required, and the episulphides can be prepared from the unsaturated fatty acids by somewhat more direct routes. Vicinal dithiocyanato fatty acids, obtained by the addition of thiocyanogen to the olefins, are converted to episulphides upon treatment with sodium sulphide or potassium hydroxide (McGhie, Ross, Julietti, and Grimwood, 1962) in accordance with equation (44). The same results are obtained upon addition of
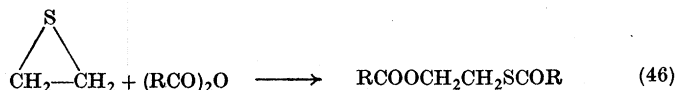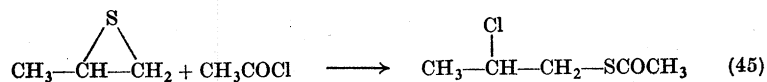
$$\underset{\diagup\diagdown}{\overset{\diagup\diagdown}{\underset{C-SCN}{\overset{C-SCN}{|}}}} \xrightarrow{\text{Na}_2\text{S or KOH}} \underset{\diagup\diagdown}{\overset{\diagup\diagdown}{\underset{C-SCN}{\overset{C-S^-}{|}}}} \longrightarrow \underset{\diagdown}{\overset{\diagup}{C}}\!\!\underset{C}{\overset{}{>}}S \qquad (44)$$
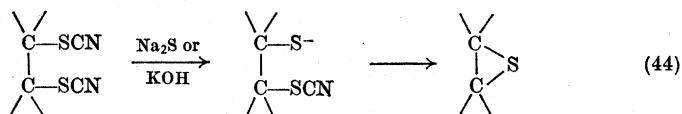
thiocyanogen chloride to the double bond and treatment of the chlorothiocyanate with base.

(d) Reactions

A recent review of the chemistry of ethylene sulphide and other low molecular weight terminal episulphides (Sander, 1966) indicates that many of the reactions of these compounds are similar to those of epoxides and in some cases similar to aziridines. All of the reactions of episulphides occur with ring-opening, and polymerisation reactions are common among the lower homologues, especially in basic media. Because of the nucleophilic nature of sulphur, many of the epithio derivatives of the lower alkanes polymerise spontaneously on storage. Unlike the nitrogen and oxygen analogues, the episulphides are readily converted to olefins either thermally or chemically by organophosphorus or organometallic compounds, and desulphurisation often occurs stereospecifically. The sulphur heterocyclics react only sluggishly with carboxylic acids, but more readily with acyl halides
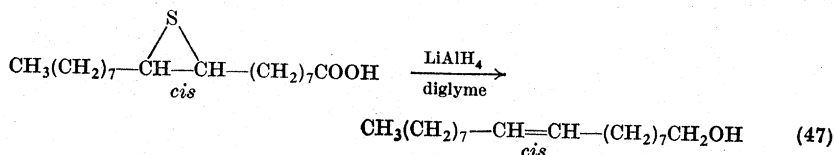
(equation (45)) or with carboxylic anhydrides (equation (46)). Reactions of episulphides with alcohols, thiols and amines have been reported, and the products are the expected mercapto ethers, thioethers and amines.

$$CH_3 \overset{\displaystyle \overset{S}{\diagup\diagdown}}{—CH—CH_2} + CH_3COCl \longrightarrow CH_3—\overset{\overset{\textstyle Cl}{|}}{CH}—CH_2—SCOCH_3 \quad (45)$$

$$\overset{\displaystyle \overset{S}{\diagup\diagdown}}{CH_2—CH_2} + (RCO)_2O \longrightarrow RCOOCH_2CH_2SCOR \quad (46)$$
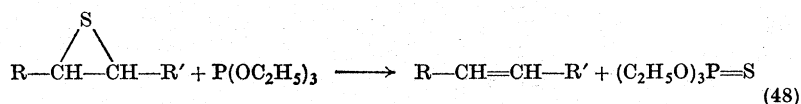
The question of orientational effects in the ring-opening reactions of unsymmetrically substituted episulphides has only begun to receive consideration recently (Schwartz, 1968). It is, of course, well known that similar reactions of the analogous epoxides and aziridines often produce mixtures of products, because the heterocyclic ring can be opened in two directions, i.e. by cleavage of either of the two dissimilar carbon-hetero-atom bonds. To the contrary, reports of ring-opening reactions of episulphides, with a few notable exceptions, indicate the formation of only one of the two possible isomers. Re-examination of the problem with the help of modern analytical tools, however, has demonstrated that both possible isomers are usually formed, and that the relative amounts of these two positional isomers depend on the usual parameters: nature of the ring-substituent, type of ring-opening reagent, pH, etc. The results indicate that attack by nucleophilic reagents on terminal episulphides, such as propylene sulphide, occurs predominantly at the less hindered carbon atom and is controlled by steric factors. Kinetic studies show (Isaacs and Neelakantan, 1968; Oddon and Wylde, 1967) that while sulphur derivatives, such as propylene sulphide, are somewhat less reactive (e.g. toward carboxylic acids or amines) than the corresponding epoxides, the isomer distribution among the products is very similar.

Epithio derivatives of fatty acids have been studied to a limited extent, but the indications are that their reactions do not differ materially from those of other episulphides. On treatment with lithium aluminium hydride in ether, only the carboxy group of *cis-* or *trans-* 9,10-epithiostearic acid is reduced and the three-membered ring remains unaffected (McGhie, Ross, Julietti, Grimwood, Usher, and Waldron, 1962). This behaviour contrasts that of the corresponding epoxy fatty acid, which is reduced to the diol under the same
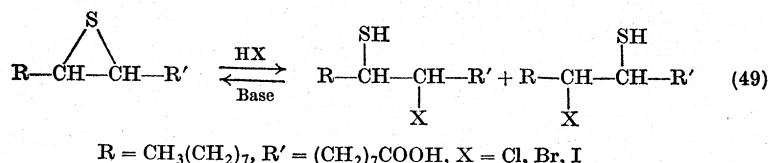
conditions. At higher temperatures, i.e. using diglyme as solvent instead of ether, the epithio derivative is reduced and desulphurised stereospecifically to unsaturated alcohol (equation (47)). When the re-

$$CH_3(CH_2)_7\text{—}\overset{\displaystyle \overset{S}{\diagup\diagdown}}{CH\text{—}CH}\text{—}(CH_2)_7COOH \quad \xrightarrow[\text{diglyme}]{\text{LiAlH}_4}$$
$$\underset{cis}{}$$

$$CH_3(CH_2)_7\text{—}\underset{cis}{CH}\text{=}CH\text{—}(CH_2)_7CH_2OH \qquad (47)$$

ducing agent is Raney Nickel in ethanol (Kannan, Roomi, Subbaram, and Achaya, 1967) the carboxy function remains unaffected, but the epithio group is desulphurised and hydrogenated. This reaction has been applied effectively to a number of *cis* and *trans* epithio fatty acids. Desulphurisation of the latter acids can also be accomplished with zinc, acetic acid, and hydrochloric acid, but the olefin produced in this manner is not stereoisomerically pure (Kaufmann and Schickel, 1963). Methyl *cis*-9,10-epithiooctadecanoate has been desulphurised with triethyl phosphite (equation (48)).

$$R\text{—}\overset{\displaystyle \overset{S}{\diagup\diagdown}}{CH\text{—}CH}\text{—}R' + P(OC_2H_5)_3 \longrightarrow R\text{—}CH\text{=}CH\text{—}R' + (C_2H_5O)_3P\text{=}S$$
$$(48)$$

Reaction with concentrated aqueous hydrogen halides in dioxan converts *cis*- and *trans*-9,10-epithiooctadecanoic acids to the corresponding mercapto halides (Roomi *et al.*, 1967) from which the original episulphides can be regenerated by treatment with base (equation (49)). On the other hand hydrochloric acid in absolute ether does not

$$R\text{—}\overset{\displaystyle \overset{S}{\diagup\diagdown}}{CH\text{—}CH}\text{—}R' \underset{\text{Base}}{\overset{\text{HX}}{\rightleftharpoons}} R\text{—}\overset{SH}{\underset{X}{\overset{|}{CH}}}\text{—}\overset{|}{CH}\text{—}R' + R\text{—}\overset{SH}{\underset{X}{\overset{|}{CH}}}\text{—}\overset{|}{CH}\text{—}R' \quad (49)$$

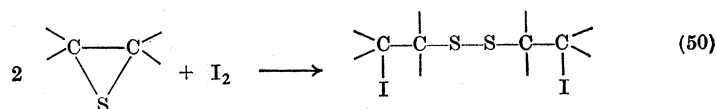$$R = CH_3(CH_2)_7, \ R' = (CH_2)_7COOH, \ X = Cl, Br, I$$

attack the episulphide function under the conditions used to determine epoxides quantitatively.

The oxidation of aliphatic episulphides to the episulphoxides with sodium periodate (Hartzell and Paige, 1966) and of phenyl-substituted episulphides to the episulphones with peracetic acid (Dittmer and Levy, 1965) has been described, but similar oxidations of fatty episulphides have not been reported. Heating with acetic acid at 120° for 2 hours

has no effect on *cis*-9,10-epithiooctadecanoic acid but readily opens the rings of the corresponding epoxides and aziridines. On the other hand, halogens attack the episulphide ring with formation of disulphides, presumably by way of an iodosulphenyliodide (equation (50)).

$$2 \quad \underset{S}{\overset{>C——C<}{\triangle}} + I_2 \longrightarrow \underset{I}{\overset{|}{>C}}—\underset{I}{\overset{|}{C}}—S—S—\underset{I}{\overset{|}{C}}—\overset{|}{C}< \qquad (50)$$
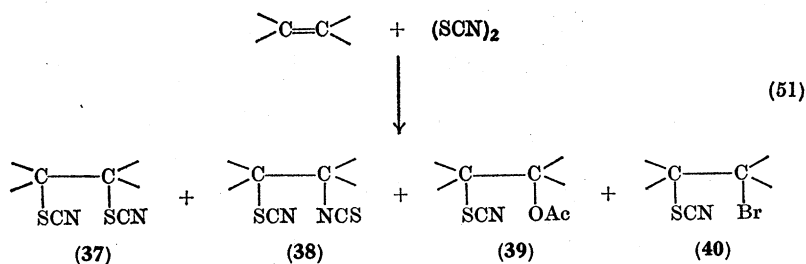
Only the surface has been scratched in the exploration of the chemistry of episulphides, and much remains to be done. Direct photochemical synthesis of epithio fatty acids, if it could be accomplished on a practical basis, would undoubtedly provide the stimulus needed for the further investigation of these interesting compounds.

3. Other Sulphur Compounds

Some reactions by which epoxy or epithio fatty acids are converted to mercapto or other bivalent sulphur derivatives of fatty acids have been described in earlier sections of this chapter. The present discussion will centre upon additional methods by which such sulphur-substituted fatty materials may be prepared.

Thiocyanogen, $(SCN)_2$, adds almost quantitatively to the double bonds of monounsaturated fatty acids, and this addition became the basis of an analytical procedure for unsaturation. Few dithiocyanato fatty acids have been isolated as pure compounds, probably because thiocyanate can act as a bidentate ligand and thus give rise to complex mixtures. Detailed studies (Russel, Silbert, and Showell, in press) of the addition reaction indicate that the products are formed according to equation (51).

$$>C=C< \quad + \quad (SCN)_2$$

$$(51)$$

$$\underset{SCN\ SCN}{\overset{>C——C<}{|\ \ \ |}} + \underset{SCN\ NCS}{\overset{>C——C<}{|\ \ \ |}} + \underset{SCN\ OAc}{\overset{>C——C<}{|\ \ \ |}} + \underset{SCN\ Br}{\overset{>C——C<}{|\ \ \ |}}$$

$$\quad (37) \qquad\qquad (38) \qquad\qquad (39) \qquad\qquad (40)$$

The dithiocyanate (37) and the thiocyanato isothiocyanate (38) are formed in approximately 7:1 ratio and are the major products.

Compounds (39) and (40) are minor by-products but may explain the lack of stoichiometry in the addition. The acetate group of (39) and bromine of (40) arise from the manner in which thiocyanogen is prepared *in situ* from lead thiocyanate and bromine in acetic acid. Nevertheless, the addition of thiocyanogen to oleic and elaidic acid has been reported (Zhila, 1959; Pogosov, Aikhodzhaev, and Ionnidis, 1964; Wood, 1946) to give dithiocyanatostearic acids in good yields. Improvements in the work-up procedure (McGhie *et al.*, 1962) make 80 per cent yields possible. The conditions for thiocyanate and iso-thiocyanate formation have been determined (Bacon, Guy, Irwin, and Robinson, 1959) to depend on olefin types and other variables.
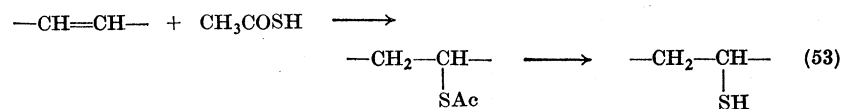
Thiocyanogen chloride and thiocyanogen iodide also add to olefins (Mesnard and Raby, 1960; 1962; Guy and Pearson, 1967), but along with the expected thiocyanato halides minor amounts of dihalogeno and dithiocyanato derivatives are obtained.

The addition of mercaptoacetic acid to unsaturated fatty acids has been studied fairly extensively (Koenig and Swern, 1957). The reaction proceeds by a free radical mechanism according to equation (52). Mercaptoacetic acid also adds to each of the two double bonds of

$$-CH{=}CH- \ + \ HSCH_2COOH \ \xrightarrow{\ h\nu\ } \ {>}CH_2{-}\underset{\underset{SCH_2COOH}{|}}{C}{<} \qquad (52)$$
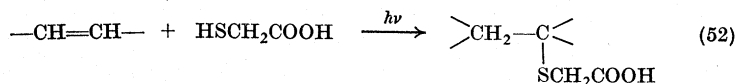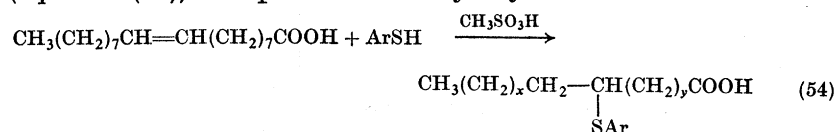
linoleic acid (Fore, O'Connor, and Goldblatt, 1958), and both mono-adducts are obtained in equal amounts. Interestingly, the remaining double bonds of the monoaddition products are predominantly *trans*, and about 12 per cent of the recovered unreacted lineolic acid has a conjugated double bond system. Moreover, a certain amount of double bond migration is observed, but the position of the substituents has not been determined. Addition of mercaptoacetic acid to a number of different monounsaturated fatty acids in each case gives two products which are distinguishable by TLC (Kannan, Subbaram, and Achaya, 1966). The addition reaction has also been proposed as a means by which unsaturated or partially unsaturated triglycerides can be removed from saturated triglycerides to permit determination of the latter (Eshelman, Manzo, Marcus, Decoteau, and Hammond, 1960). However, with the increase in sophistication in chromatographic techniques in the last decade this method may not experience wide-spread application in the future. With thioacetic acid, methyl oleate gives methyl 9(10)-acetylmercaptostearate which yields mercapto-

stearic acid when hydrolysed (Koenig, Sasin, and Swern, 1958; equation (53)).

$$—CH=CH— + CH_3COSH \longrightarrow$$

$$—CH_2—\underset{\underset{SAc}{|}}{CH}— \longrightarrow —CH_2—\underset{\underset{SH}{|}}{CH}— \quad (53)$$

Aromatic thiols add to unsaturated fatty acids in a reaction which is catalysed by methanesulphonic acid and which is undoubtedly ionic in nature (Eisner, Perlstein, and Ault, 1962; Ault and Eisner, 1965) (equation (54)). The products are alkyl aryl thioethers, which, unlike
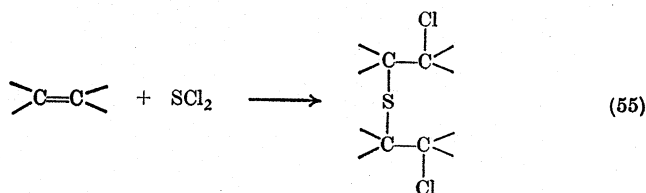
$$CH_3(CH_2)_7CH=CH(CH_2)_7COOH + ArSH \xrightarrow{CH_3SO_3H}$$

$$CH_3(CH_2)_xCH_2—\underset{\underset{SAr}{|}}{CH}(CH_2)_yCOOH \quad (54)$$

their oxygen analogues, do not rearrange to form new carbon–carbon bonds. In view of the strong acid medium used, it seems likely that a considerable amount of carbonium ion migration occurs, but substituent locations have not yet been determined.
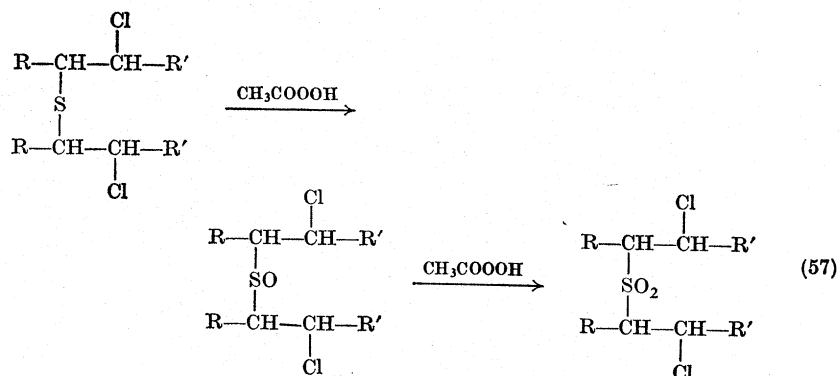
The free radical addition of hydrogen sulphide and of alkane dithiols to methyl oleate and to other unsaturated fatty esters can be accomplished by irradiation at room temperature or below (Schwab, Gast, and Cowan, 1968). Low yields of products having elemental compositions approximating those of simple addition compounds are obtained, but pure species have not been isolated.

The addition of sulphur and of sulphur–chlorine compounds to unsaturated oils has been practiced for some time in the production of commercial materials suitable as lubricant components, plasticisers, and rubber-like products (Markley, 1964; Zajic, Zalud, and Kopecka, 1964). The nature of the adducts has been the subject of conjecture, but systematic structure investigations have been rare, and the product mixtures usually have been complex. Under suitable conditions, however, simple, well-defined chemical entities can be formed. For instance, the reaction of sulphur dichloride at low temperature with oleate and elaidate esters and with oleyl nitrile (Grimm, 1967) has been demonstrated to produce β,β-dichloroalkyl sulphides according to equation (55). This reaction is, of course, entirely analogous to the well-known addition of the same reagent to ethylene with the formation of mustard gas (equation (56)).

The β,β-dichloroalkyl sulphides produced from fatty derivatives, such as methyl oleate, can be oxidised to sulphoxides and sulphones

$$>C=C< \quad + \quad SCl_2 \quad \longrightarrow \quad \begin{array}{c} Cl \\ | \\ >C-C< \\ | \\ S \\ | \\ >C-C< \\ | \\ Cl \end{array} \qquad (55)$$

$$CH_2{=}CH_2 \quad + \quad SCl_2 \quad \longrightarrow \quad (ClCH_2CH_2)_2S \qquad (56)$$

with peroxyacetic acid (equation (57)). The chlorine atoms of the β,β-dichloroalkyl sulphides are replaceable by nucleophiles such as ammonia, amines, azide, hydroxide, etc. (Grimm, 1967).

$$\begin{array}{c} Cl \\ | \\ R{-}CH{-}CH{-}R' \\ | \\ S \\ | \\ R{-}CH{-}CH{-}R' \\ | \\ Cl \end{array} \quad \xrightarrow{CH_3COOOH} \quad$$

$$\begin{array}{c} Cl \\ | \\ R{-}CH{-}CH{-}R' \\ | \\ SO \\ | \\ R{-}CH{-}CH{-}R' \\ | \\ Cl \end{array} \quad \xrightarrow{CH_3COOOH} \quad \begin{array}{c} Cl \\ | \\ R{-}CH{-}CH{-}R' \\ | \\ SO_2 \\ | \\ R{-}CH{-}CH{-}R' \\ | \\ Cl \end{array} \qquad (57)$$

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